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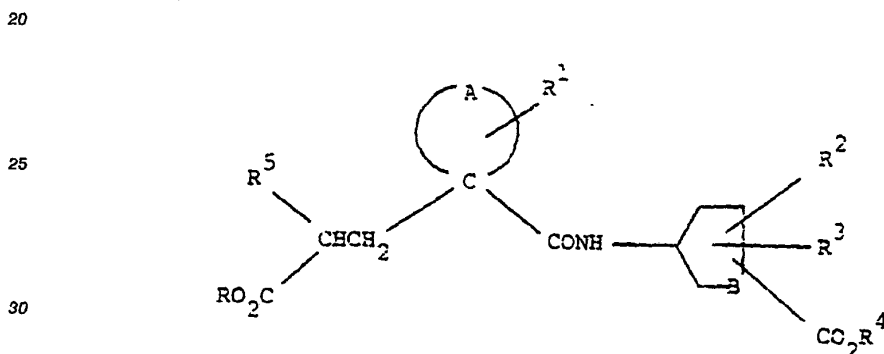
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## Description

This invention relates to a series of spiro-substituted glutaramide derivatives which are diuretic agents having utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as hypertension and heart failure.

The compounds are inhibitors of the zinc-dependent, neutral endopeptidase E.C.3.4.24.11. This enzyme is involved in the breakdown of several peptide hormones, including atrial natriuretic factor (ANF), which is secreted by the heart and which has potent vasodilatory, diuretic and natriuretic activity. Thus, the compounds of the invention, by inhibiting the neutral endopeptidase E.C.3.4.24.11, can potentiate the biological effects of ANF. Thus, in particular the compounds are diuretic agents having utility in the treatment of a number of disorders, including hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menière's disease, hyperaldosteronism (primary and secondary) and hypercalciuria. In addition, because of their ability to potentiate the effects of ANF the compounds have utility in the treatment of glaucoma. As a further result of their ability to inhibit the neutral endopeptidase E.C.3.4.24.11 the compounds of the invention may have activity in other therapeutic areas including for example the treatment of asthma, inflammation, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhoea and irritable bowel syndrome), the modulation of gastric acid secretion and the treatment of hyperreninaemia.

The compounds are of the formula:



(I)

wherein

A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring;

B is  $(CH_2)_m$  wherein m is an integer of from 1 to 3;

each of R and R<sup>4</sup> is independently H, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl or an alternative biolabile ester-forming group;

R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> and R<sup>3</sup> are each independently H, OH, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy;

and

R<sup>5</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, aryl(C<sub>2</sub>-C<sub>6</sub> alkynyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup> or a saturated heterocyclic group;

or C<sub>1</sub>-C<sub>6</sub> alkyl substituted by one or more substituents chosen from halo, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> hydroxyalkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy(C<sub>1</sub>-C<sub>6</sub> alkoxy), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, aryl, aryloxy, aryloxy(C<sub>1</sub>-C<sub>4</sub> alkoxy), heterocyclyl, heterocyclyloxy, -NR<sup>6</sup>R<sup>7</sup>, NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -SH, -S(O)<sub>p</sub>R<sup>10</sup>, -COR<sup>11</sup> or -CO<sub>2</sub>R<sup>12</sup>;

wherein

R<sup>6</sup> and R<sup>7</sup> are each independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl (optionally substituted by hydroxy or C<sub>1</sub>-C<sub>4</sub> alkoxy), aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), C<sub>2</sub>-C<sub>6</sub> alkoxyalkyl, or heterocyclyl; or the two groups R<sup>6</sup> and R<sup>7</sup> are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C<sub>1</sub>-C<sub>4</sub> alkyl)-piperazinyl group;

R<sup>8</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

$R^9$  is  $C_1$ - $C_4$  alkyl,  $CF_3$ , aryl, aryl( $C_1$ - $C_4$  alkyl), aryl( $C_1$ - $C_4$  alkoxy), heterocycyl,  $C_1$ - $C_4$  alkoxy or  $NR^6R^7$  wherein  $R^6$  and  $R^7$  are as previously defined;

$R^{10}$  is  $C_1$ - $C_4$  alkyl, aryl, heterocycyl or  $NR^6R^7$  wherein  $R^6$  and  $R^7$  are as previously defined;

$R^{11}$  is  $C_1$ - $C_4$  alkyl,  $C_3$ - $C_7$  cycloalkyl, aryl or heterocycyl;

5  $R^{12}$  is H or  $C_1$ - $C_4$  alkyl;

and

p is 0, 1 or 2;

and pharmaceutically acceptable salts thereof and bioprecursors therefor.

10 In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms may be straight or branched-chain. The term aryl as used herein means an aromatic hydrocarbon group such as phenyl or naphthyl which may optionally be substituted with, for example, one or more OH, CN,  $CF_3$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halo, carbamoyl, aminosulphonyl, amino, mono or di( $C_1$ - $C_4$  alkyl) amino or ( $C_1$ - $C_4$  alkanoyl)amino groups. Halo means fluoro, chloro, bromo or iodo.

15 The term heterocycyl means a 5 or 6 membered nitrogen, oxygen or sulphur containing heterocyclic group which, unless otherwise stated, may be saturated or unsaturated and which may optionally include a further oxygen or one to three nitrogen atoms in the ring and which may optionally be benzofused or substituted with for example, one or more halo,  $C_1$ - $C_4$  alkyl, hydroxy, carbamoyl, benzyl, oxo, amino or mono or di( $C_1$ - $C_4$  alkyl)amino or ( $C_1$ - $C_4$  alkanoyl)amino groups. Particular examples of heterocycles include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, 20 tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, indolyl, isoindolyl, quinolyl, quinoxalyl, quinazolinyl and benzimidazolyl, each being optionally substituted as previously defined.

25 The compounds of formula (I) may contain several asymmetric centres and thus they can exist as enantiomers and diastereomers. The invention includes both the separated individual isomers as well as mixtures of isomers.

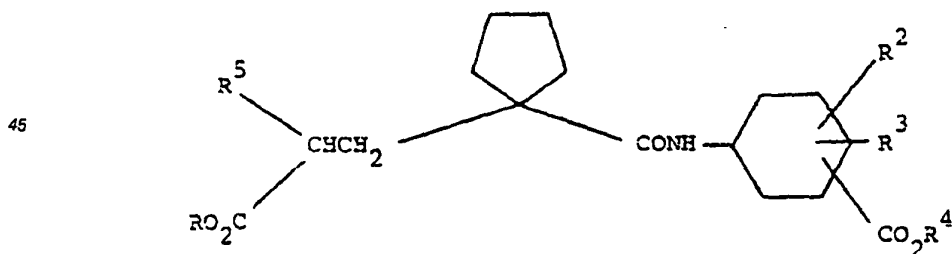
30 The pharmaceutically acceptable salts of the compounds of formula (I) containing an acidic centre are those formed with bases which form non-toxic salts. Examples include the alkali metal salts such as the sodium, potassium or calcium salts or salts with amines such as diethylamine. Compounds having a basic centre can also form acid addition salts with pharmaceutically acceptable acids. Examples include the hydrochloride hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate and tartrate salts.

The term bioprecursor in the above definition means a pharmaceutically acceptable biologically degradable derivative of the compounds of formula (I) which, upon administration to an animal or human being, is converted in the body to produce a compound of the formula (I).

35 One group of preferred compounds of formula (I) are those compounds wherein A is  $(CH_2)_n$ , and n is an integer of from 3 to 6 and wherein each of R and  $R^4$  is independently H,  $C_1$ - $C_6$  alkyl or benzyl.

A particularly preferred group of compounds of the formula (I) are those wherein A is  $(CH_2)_4$ ,  $R^1$  is H and B is  $(CH_2)_2$ , i.e. compounds of the formula (II) wherein R,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as previously defined for formula (I):

40



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(II)

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Also preferred are those compounds of formulae (I) and (II) wherein R and  $R^4$  are both H (diacids) as well as biolabile mono and di-ester derivatives thereof wherein one or both of R and  $R^4$  is a biolabile ester-

forming group.

The term biolabile ester-forming group is well understood in the art as meaning a group which provides an ester which can be readily cleaved in the body to liberate the corresponding diacid of formula (I) wherein R and R<sup>4</sup> are both H. A number of such ester groups are well known, for example in the penicillin area or in the case of the ACE-inhibitor antihypertensive agents.

In the case of the compounds of formulae (I) and (II) such biolabile pro-drug esters are particularly advantageous in providing compounds of the formula (I) suitable for oral administration. The suitability of any particular ester-forming group can be assessed by conventional animal or in vitro enzyme hydrolysis studies. Thus, desirably for optimum effect, the ester should only be hydrolysed after absorption, accordingly, the ester should be resistant to hydrolysis before absorption by digestive enzymes but should be readily hydrolyzed by for example, liver enzymes. In this way the active diacid is released into the bloodstream following oral absorption.

In addition to lower alkyl esters (particularly ethyl) and benzyl esters, suitable biolabile esters include alkanoyloxyalkyl esters, including alkyl, cycloalkyl and aryl substituted derivatives thereof, aroyloxyalkyl esters, arylestere, aralkylesters, and haloalkyl esters wherein said alkanoyl or alkyl groups have 1 to 8 carbon atoms and are branched or straight chain and said aryl groups are phenyl, naphthyl or indanyl optionally substituted with one or more C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy groups or halo atoms.

Thus examples of R and R<sup>4</sup> when they are biolabile ester-forming groups other than ethyl and benzyl include:

- 1-(2,2-diethylbutyryloxy)ethyl
- 2-ethylpropionyloxymethyl
- 1-(2-ethylpropionyloxy)ethyl
- 1-(2,4-dimethylbenzoyloxy)ethyl
- $\alpha$ -benzoyloxybenzyl
- 1-(benzoyloxy)ethyl
- 2-methyl-1-propionyloxy-1-propyl
- 2,4,6-trimethylbenzoyloxymethyl
- 1-(2,4,6-trimethylbenzoyloxy)ethyl
- pivaloyloxymethyl
- phenethyl
- phenpropyl
- 2,2,2-trifluoroethyl
- 1- or 2-naphthyl
- 2,4-dimethylphenyl
- 4-t-butylphenyl

and

5-indanyl.

Of these a particularly preferred biolabile ester-forming group is 5-indanyl.

Compounds of the formulae (I) and (II) wherein one or both of R and R<sup>4</sup> are C<sub>1</sub>-C<sub>6</sub> alkyl, particularly ethyl, or benzyl, are also active by virtue of their hydrolysis in vivo, and, in addition, are valuable intermediates for the preparation of the diacids wherein R and R<sup>4</sup> are both H. The mono-benzyl and mono-ethyl esters in particular have been found to be rapidly hydrolysed in vivo to give the diacid.

In a further group of preferred compounds of formula (II), R is H, R<sup>2</sup> is H, R<sup>3</sup> is CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub> and R<sup>4</sup> is H. Particularly preferred are those compounds wherein R, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each H and the carboxy group CO<sub>2</sub>R<sup>4</sup> is attached at the 3- or 4-position of the cyclohexane ring, most especially those compounds having cis-stereochemistry relative to the amide group.

Of particular interest because of their good oral activity are the mono-ethyl esters of formula (II) wherein R, R<sup>2</sup> and R<sup>3</sup> are each H, R<sup>4</sup> is ethyl, and wherein the ethoxycarbonyl group is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group.

The group R<sup>5</sup> is preferably C<sub>2</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>5</sub> alkynyl, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, C<sub>5</sub>-C<sub>6</sub> cycloalkenyl, C<sub>1</sub>-C<sub>4</sub> alkylsulphonamido, or tetrahydrofuranyl or wherein R<sup>5</sup> is C<sub>1</sub>-C<sub>3</sub> alkyl substituted by C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy(C<sub>2</sub>-C<sub>4</sub> alkoxy), C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 4-pyridyl, 2-imidazolyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, C<sub>2</sub>-C<sub>4</sub> alkoxy-carbonylamino, C<sub>1</sub>-C<sub>4</sub> alkylsulphonyl, C<sub>1</sub>-C<sub>4</sub> alkylsulphonamido, arylsulphonamido, heteroarylsulphonamido or benzoylamino.

Thus in one particular and preferred aspect, the invention provides dicarboxylic acids of the formula (II) wherein R and R<sup>4</sup> are both H, and wherein R<sup>2</sup> and R<sup>3</sup> are both H, the group CO<sub>2</sub>R<sup>4</sup> is attached at the 4-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group and wherein R<sup>5</sup> is n-propyl, methoxyethyl, 2-methoxyethoxymethyl, 2-butyryl, cyclohexenyl, tetrahydrofuranyl, 4-pyridyl-

methyl, 2-imidazolylmethyl, acetonyl, ethylsulphonylmethyl, benzenesulphonamidomethyl, n-propylsulphonamido or 1-methoxycarbonylaminoethyl.

Particularly preferred individual compounds include 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(n-propyl)propanoic acid.

- 5 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethyl)propanoic acid.  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid.  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-butynyl)propanoic acid.  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(3-tetrahydrofuranyl)propanoic acid.  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(n-propylsulphonamido)propanoic acid.

- 10 In another particular and preferred aspect, the invention provides dicarboxylic acids of the formula (II) wherein R and R<sup>4</sup> are both H, R<sup>2</sup> and R<sup>3</sup> are both H, the group CO<sub>2</sub>R<sup>4</sup> is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group and wherein R<sup>5</sup> is n-propyl, 2-methoxyethoxymethyl, 2-butynyl, 2-propenyl, 2-butenyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclopropylmethyl, tetrahydrofuranyl, 4-pyridylmethyl, n-propylsulphonylamino, benzenesulphonylaminoethyl, or benzoylaminoethyl.

- 15 Particularly preferred individual compounds include 3-{1-[(cis-3-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(n-propyl)propanoic acid,

- 3-{1-[(cis-3-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid,  
 3-{1-[(cis-3-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-butynyl)propanoic acid, and  
 20 3-{1-[(cis-3-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(n-propylsulphonamido)propanoic acid.

- In a further particular and preferred aspect, the invention provides mono ethyl esters of the formula (II) wherein R is H and R<sup>4</sup> is ethyl and wherein R<sup>2</sup> and R<sup>3</sup> are both H, the ethoxycarbonyl group is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry and R<sup>5</sup> is 2-methoxyethoxymethyl, n-propyl, 2-butynyl, 2-propenyl, cyclohexenyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, tetrahydrofuranyl,  
 25 4-pyridylmethyl, benzenesulphonamidomethyl, benzoylaminoethyl, or n-propylsulphonamido.

Particularly preferred individual compounds include 3-{1-[(cis-3-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid.

- 3-{1-[(cis-3-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(n-propyl)propanoic acid,  
 3-{1-[(cis-3-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(2-butynyl)propanoic acid, and  
 30 3-{1-[(cis-3-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(n-propylsulphonamido)propanoic acid.

In a yet further particular and preferred aspect, the invention provides biolabile ester derivatives of formula (II) wherein one or both of R and R<sup>4</sup> is 5-indanyl.

Particularly preferred individual compounds include:

- 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid 5-in-  
 35 danyl ester, and  
 3-{1-[(cis-4-{5-indanyloxy}carbonyl)cyclohexyl]carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid.

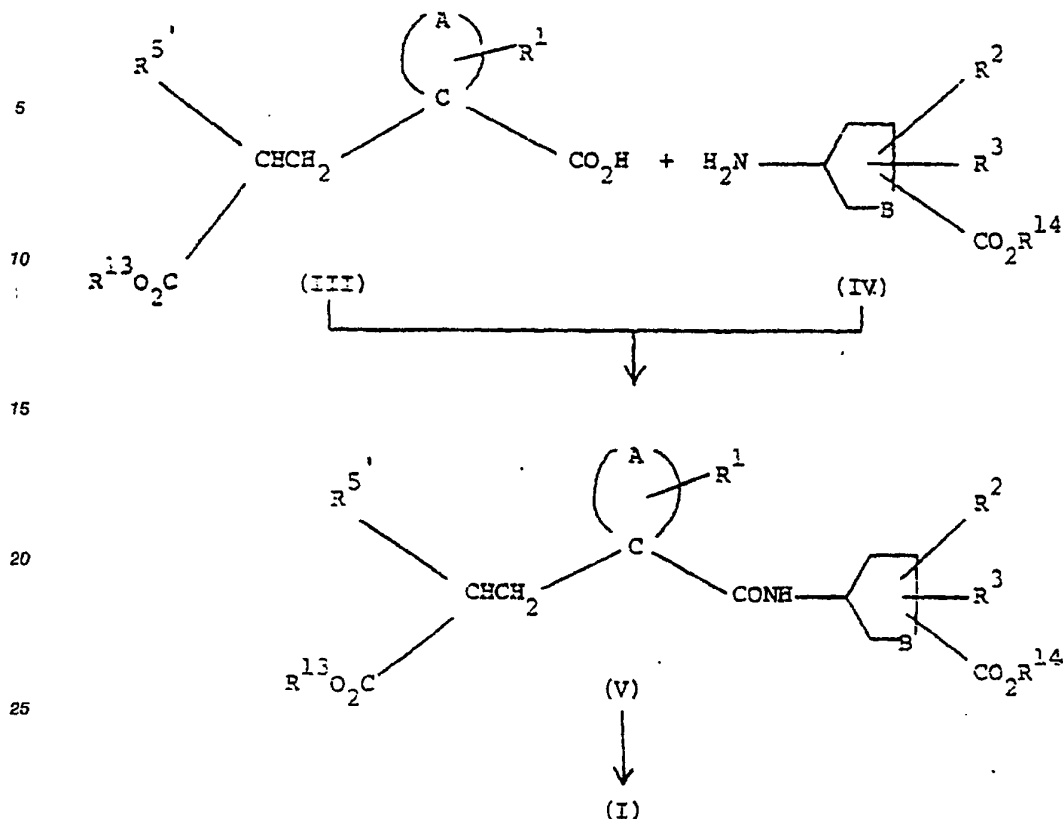
- The compounds of formula (I) are prepared by a number of different processes. The basic procedure involves the synthesis of a partially protected spiro-substituted glutaric acid derivative which is coupled to an amine to give the desired glutaramide. The carboxylic acid group in the amine, if free, or any reactive groups in R<sup>5</sup>, may require protection during the coupling step and such protecting groups are removed in the final stage of the process.

- The synthetic route is illustrated in scheme 1 wherein A, B, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as previously defined, R<sup>5'</sup> is as defined for R<sup>5</sup> with any reactive group therein protected if necessary and R<sup>13</sup> and R<sup>14</sup> are as defined for R and R<sup>4</sup> excluding H, or they are conventional carboxylic acid protecting groups:

#### Scheme 1

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The reaction of the compounds of formula (III) and (IV) is achieved using conventional amide coupling techniques. Thus in one process the reaction is achieved with the reactants dissolved in an organic solvent, e.g. dichloromethane, using a diimide condensing agent, for example 1-ethyl-3-(dimethylaminopropyl)-carbodiimide, or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of 1-hydroxybenzotriazole and an organic base such as N-methylmorpholine. The reaction is generally complete after a period of from 12 to 24 hours at room temperature and the product is then isolated by conventional procedures, i.e. by washing with water or filtration to remove the urea biproduct and evaporation of the solvent. The product may be further purified by crystallisation or chromatography, if necessary. The compounds of formula (V) include compounds of formula (I) wherein R and R<sup>4</sup> are C<sub>1</sub>-C<sub>6</sub> alkyl or benzyl.

In some cases the coupled product, in protected form, may be subjected to conventional chemical transformation reactions to allow preparation of further compounds of formula (V). Thus for example compounds of formula (V) wherein R<sup>5</sup> contains an ester group may be hydrolysed or hydrogenated to generate the carboxylic acid which may be further reacted, for example with an amine, to give amide derivatives.

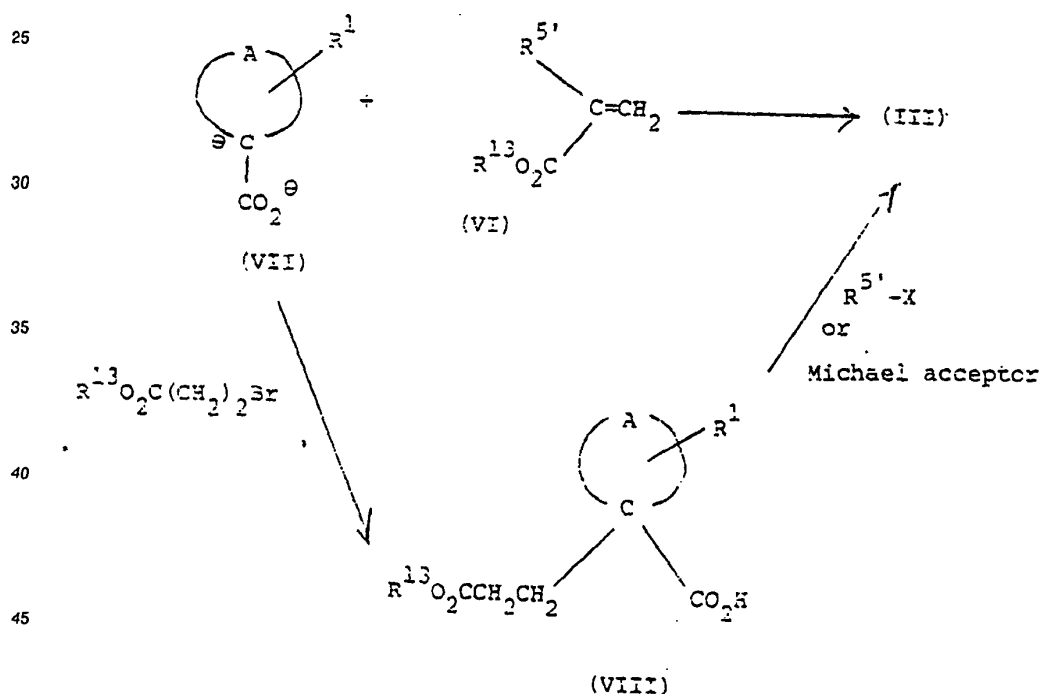
Similarly compounds wherein R<sup>5</sup> contains a substituted or protected amino group (for example a benzylamino, dibenzylamino, benzyloxycarbonylamino or t-butyloxycarbonylamino group) may be converted to the free amines by hydrogenation or hydrolysis as appropriate. The amines produced may be further reacted, thus for example reaction with a sulphonyl halide yields the corresponding sulphonamides, acylation with an acid chloride or anhydride yields the corresponding amides, reaction with an isocyanate yields urea derivatives and reaction with a chloroformate or N-(aryloxycarbonyl)succinimide yields the alkoxycarbonylamino and aryloxycarbonylamino products respectively. Other reactions include, for example, oxidation of a sulphide to yield the corresponding sulfoxide or sulphone derivative; Wacker oxidation of a terminal olefin to give the corresponding methyl ketone which in turn may be further reacted, for example by reductive amination to yield the corresponding amine; hydrogenation of a benzyloxy containing compound to yield the alcohol, reduction of an azide group to give an amine, or reduction of a cycloalkene to a cycloalkane. All these transformations are entirely conventional and appropriate conditions and reagents for their performance will be well known to those skilled in the art as will other variations and possibilities.

The diesters of formula (V) may be further reacted to give the monoester or diacid derivatives of formula (I) wherein one or both of R and R<sup>4</sup> are H. The conditions used will depend on the precise nature of the groups R<sup>13</sup> and R<sup>14</sup> present in the compound of formula (V) and a number of variations are possible. Thus for example when both of R<sup>13</sup> and R<sup>14</sup> are benzyl, hydrogenation of the product will yield the diacid of formula (I) wherein R and R<sup>4</sup> are both H. Alternatively if one of R<sup>13</sup> and R<sup>14</sup> is benzyl and the other is alkyl, hydrogenation will yield a monoester product. This can then be hydrolysed, if desired, to again yield the diacid product. When one of R<sup>13</sup> and R<sup>14</sup> is t-butyl, treatment of the compound of formula (V) with trifluoroacetic acid yields the corresponding acid. The diester product wherein R<sup>13</sup> and R<sup>14</sup> are benzyl or lower alkyl can also be treated with trimethylsilyl iodide to produce the dicarboxylic acid product. If some other carboxylic acid protecting group is used for R<sup>13</sup> or R<sup>14</sup> then clearly appropriate conditions for its removal must be employed in the final step to give the ester or diacid product of formula (I). In the case where the ring A or the substituent R<sup>5</sup> is unsaturated, the deprotection must be effected by non-reductive methods, thus for example if either of R and R<sup>4</sup> is benzyl, they may be removed by treatment with trimethylsilyl iodide.

As well as removing any protecting group which may be present in R<sup>5</sup>, a number of chemical transformation reactions are possible on the final mono-ester or diacid products as previously described. In each case the product may be obtained as the free carboxylic acid or it may be neutralised with an appropriate base and isolated in salt form.

The starting spiro-substituted glutaric acid mono esters of formula III may be prepared by a number of different processes as illustrated by the following reaction scheme:

Scheme 2



The acrylates of formula (VI) are either known compounds which are commercially available or they may be prepared by conventional methods in accordance with literature methods (for example by reaction of an appropriately substituted malonic acid mono-ester with paraformaldehyde with concomitant decarboxylation).

The acrylate is reacted directly with the dianion derived from the appropriate cycloalkane or cycloalkene carboxylic acid by treatment with a strong base (e.g. lithium diisopropylamide) to give the glutaric acid mono ester of formula (III). Alternatively, the acid is reacted with a 3-bromopropionate to give the corresponding ester (VIII). This is then alkylated by reaction with a strong base (e.g. lithium

diisopropylamide) at low temperature to generate the dianion followed by addition of the appropriate compound of formula  $R^5-X$ , (wherein X is a leaving group, e.g. trifluoromethane sulphonyloxy or halo, preferably bromo), or a Michael addition acceptor (e.g. a vinyl sulphone) to again yield the glutaric acid mono ester of formula (III).

- 5 The amines of formula (IV) are generally known compounds which are commercially available or they may be prepared by conventional methods in accordance with literature methods (for example, in the case where B is  $(CH_2)_2$ , by reduction of the corresponding benzoic acid).

Compounds of the formula (I) wherein one or both of R and  $R^4$  is a biolabile ester forming group are prepared following similar procedures to those described above.

- 10 Thus, in one variant of the process outlined in Scheme 1, a compound of formula (III) wherein  $R^{13}$  is a biolabile ester-forming group is coupled to the appropriate compound of formula (IV) wherein  $R^{14}$  is a benzyl group, and the product is hydrogenated to give the compound of formula (I) wherein R is a biolabile ester-forming group and  $R^4$  is H.

- The glutaric mono esters of formula (III) wherein  $R^{13}$  is a biolabile ester-forming group are prepared from the corresponding compounds of formula (III) wherein  $R^{13}$  is a conventional selectively removable carboxylic acid protecting group, for example t-butyl, by first protecting the free carboxyl group, for example as its phenacyl ester; removing  $R^{13}$  by conventional methods appropriate to the particular protecting group employed; forming an ester with the desired biolabile ester-forming group, for example by reaction with a halide of formula  $R^{17}X'$  or by reaction with an alcohol of formula  $R^{17}OH$  and a diimide  
20 condensing agent, wherein  $R^{17}$  is a biolabile ester-forming group and  $X'$  is chloro, bromo or iodo, preferably chloro; and finally removing the phenacyl protecting group by conventional procedures, for example by reaction with zinc and glacial acetic acid.

- The product is then reacted with the amine of formula (IV) using the coupling techniques previously described and the benzyl group  $R^{14}$  is finally removed by a conventional catalytic hydrogenation to give the  
25 product of formula (I) wherein R is a biolabile ester-forming group and  $R^4$  is H.

- In an alternative variant of this process, an amine of formula (IV) wherein  $R^{14}$  is a biolabile ester-forming group is coupled with a compound of formula (III) wherein  $R^{13}$  is a conventional selectively removable protecting group, for example a benzyl group. The coupled product is then deprotected; thus in the case where  $R^{13}$  is benzyl, the product is hydrogenated to give the compound of formula (I) wherein R is H and  
30  $R^4$  is a biolabile ester-forming group.

- In an alternative process, compounds of the formula (I) wherein one of R and  $R^4$  is a biolabile ester-forming group, are prepared from the appropriate compound of formula (V) wherein  $R^{13}$  and  $R^{14}$  are both selectively removable protecting groups by deprotection to remove one of  $R^{13}$  or  $R^{14}$  followed by esterification, for example by reaction with a halide of formula  $R^{17}X'$  wherein  $R^{17}$  and  $X'$  are as previously  
35 defined, and finally removing the other protecting group to give the mono ester product.

- Thus in one variant of this procedure, the compound of formula (V) wherein  $R^{13}$  is t-butyl and  $R^{14}$  in benzyl is deprotected with trifluoroacetic acid to give the compound of formula (I) wherein R is H and  $R^4$  is benzyl. Esterification is achieved by, for example, first converting the mono-benzyl ester to its caesium salt by neutralising with caesium carbonate, followed by reaction with the halide of formula  $R^{17}X$  by stirring in  
40 an inert organic solvent, for example dimethylformamide, for an overnight period. The benzyl group  $R^4$  is then removed by a conventional catalytic hydrogenation to give the compound of formula (I) wherein R is a biolabile ester-forming group and  $R^4$  is H.

- In an alternative variant of this procedure  $R^{14}$  is removed from the compound of formula (V), esterification and deprotection gives the compound of formula (I) wherein R is H and  $R^4$  is an biolabile  
45 ester-forming group.

Finally, in a further process, compounds wherein both of R and  $R^4$  are biolabile ester-forming groups may be prepared from the corresponding diacid of formula (I) wherein both of R and  $R^4$  are H by a single esterification step, for example by reaction with a halide of formula  $R^{17}X$  as previously described or by reaction with an alcohol in the presence of a carbodiimide coupling agent.

- 50 Appropriate coupling and protecting methods for all of the above steps and alternative variations and procedures will be well known to those skilled in the art by reference to standard text books and to the examples provided hereinafter.

- As previously mentioned, the compounds of the invention are potent inhibitors of the neutral endopeptidase (E.C.3.4.24.11). This enzyme is involved in the breakdown of a number of peptide hormones and, in particular we have discovered that it is involved in the breakdown of atrial natriuretic factor (ANF). This hormone consists of a family of related natriuretic peptides, secreted by the heart, of which the major circulating form in humans is known to be the 28 amino-acid peptide referred to as  $\alpha$ -hANP (see for example G. A. Sagnella and G. A. MacGreggor, Nature, 1984 309, 666 and S. A. Atlas and others, Nature,  
55



1984, 309, 717-725). Thus, the compounds of the invention, by preventing the degradation of ANF by endopeptidase E.C.3.4.24.11, can potentiate its biological effects and the compounds are thus diuretic and natriuretic agents of utility in a number of disorders as previously described.

Activity against neutral endopeptidase E.C.3.4.24.11 is assessed using a procedure based on the assay described by J. T. Gafford, R. A. Skidgel, E. G. Erdos and L. B. Hersh, *Biochemistry*, 1983, 32, 3265-3271. The method involves determining the concentration of compound required to reduce by 50% the rate of release of radiolabelled hippuric acid from hippuryl-L-phenylalanyl-L-arginine by a neutral endopeptidase preparation from rat kidney.

The activity of the compounds as diuretic agents is determined by measuring their ability to increase urine output and sodium ion excretion in saline loaded conscious mice. In this test, male mice (Charles River CD1, 22-28 g) are acclimatised and starved overnight in metabowls. The mice are dosed intravenously via the tail vein, with the test compound dissolved in a volume of saline solution equivalent to 2.5% of body weight. Urine samples are collected each hour for two hours in pre-weighed tubes and analysed for electrolyte concentration. Urine volume and sodium ion concentration from the test animals are compared to a control group which received only saline.

For administration to man in the curative or prophylactic treatment of hypertension, congestive heart failure or renal insufficiency, oral dosages of the compounds will generally be in the range of from 10-1500 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2 to 300 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier for administration singly, or in multiple doses, once or several times a day. Dosages for intravenous administration would typically be within the range 5 to 500 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

The compounds may be administered alone but may also be administered together with such other agents as the physician shall direct to optimise control of blood pressure or to treat congestive heart failure, renal insufficiency or other disorders in any particular patient in accordance with established medical practice. Thus the compounds can be co-administered with a variety of cardiovascular agents, for example with an ACE inhibitor such as captopril or enalapril to facilitate the control of blood pressure in treatment of hypertension; or with digitalis, or another cardiac stimulant or with an ACE inhibitor, for the treatment of congestive heart failure. Other possibilities include co-administration with a calcium antagonist (e.g. nifedipine or diltiazem) a beta-blocker (e.g. atenolol) or an alpha-blocker (e.g. prazosin) as shall be determined by the physician as appropriate for the treatment of the particular patient or condition involved.

In addition to the above, the compounds may also be administered in conjunction with exogenous ANF, or a derivative thereof or related peptide or peptide fragment having diuretic/natriuretic activity or with other ANF-gene related peptides (e.g. as described by D. L. Vesely et al, *Biochem. Biophys. Res. Comm.*, 1987, 143, 186).

Thus in a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I) or (II), or a pharmaceutically acceptable salt thereof or bioprecursor thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also includes a compounds of the formula (I) or (II), or a pharmaceutically acceptable salt thereof or bioprecursor thereof, for use in medicine, in particular in the treatment of hypertension, congestive heart failure or renal insufficiency in a human being.

Finally, based on out discovery that the neutral endopeptidase E.C.3.4.24.11 is involved in the breakdown of atrial natriuretic factor (ANF) and that compounds which are inhibitors of neutral endopeptidase E.C.3.4.24.11 can be used to prevent degradation of ANF by endopeptidase E.C.3.4.24.11 and thus potentiate its diuretic and natriuretic activity; the invention includes the use of a compound having the ability to inhibit the neutral endopeptidase E.C.3.4.24.11 for the manufacture of a medicament to prevent degradation of ANF and thus potentiate its diuretic and natriuretic action in the treatment of hypertension,

heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menière's disease, hyperaldosteronism (primary and secondary), hypercalciuria or glaucoma.

The preparation of the compounds of the invention and of intermediates for use in their preparation is illustrated by the following Examples, in which Example 1 - 14 describe the preparation of certain starting materials of formula (VI), Examples 15-69 describe the preparation of glutaric acid derivatives of formula (III), Examples 70-80 describe the preparation of certain amine starting materials of formula (IV), Examples 81-216 describe the preparation of diesters of formula (V), Examples 217-405 and 429-432 describe the preparation of mono and dicarboxylic acids of formula (I) wherein one or both of R and R<sup>4</sup> is H, and Examples 406-428 describe the preparation of various pro-drug esters where one or both of R and R<sup>4</sup> is a biolabile ester-forming group.

#### EXAMPLE 1

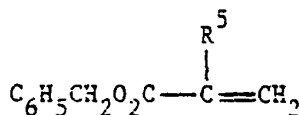
##### 2-(2-Methoxyethyl)propenoic acid benzyl ester

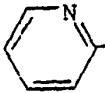
Dibenzyl malonate (28.43 g, 0.1 mole) was added dropwise over 1 hour to a stirred suspension of sodium hydride (3.15 g, 80% dispersion in oil; 0.105 mole) in dry tetrahydrofuran (100 ml) under nitrogen, the temperature being allowed to rise to 40 °C. 2-Methoxyethyl bromide (13.9 g, 0.1 mole) was added to the resulting clear solution, which was stirred at room temperature for two hours, and then refluxed overnight. Water was added, and the mixture extracted with methylene chloride. The organic extract on washing with water, drying (MgSO<sub>4</sub>) and evaporation under vacuum gave a crude liquid (30.94 g). Chromatography on silica gel (700 g) eluting with a mixture of ether and hexane (2:8 by volume) gave 2-methoxyethyl-malonic acid dibenzyl ester as a colourless liquid (15.6 g). This was dissolved in dioxan (150 ml) and a solution of potassium hydroxide (2.55 g, 45.44 mmole) in water (40 ml) added at 0 °C with stirring. The mixture was stirred overnight at room temperature and the solvent was evaporated under vacuum. Water was added and the mixture was extracted with ether to remove unreacted diester. The aqueous phase was then acidified with 2N hydrochloric acid (50 ml) and extracted with ether. The organic extract on washing with water, drying (MgSO<sub>4</sub>) and evaporation under vacuum gave the mono-ester as a colourless oil (8.95 g, 78%).

Paraformaldehyde (1.6 g, 53.34 mmole) was added to a stirred solution of the crude mono-ester (8.95 g, 35.48 mmole) and piperidine (502 mg, 5.9 mmole) in pyridine (70 ml). After stirring at 60 °C for two and a half hours, the mixture was cooled, poured onto ice, acidified with concentrated hydrochloric acid, and extracted with ether. The organic extract was sequentially washed with water, saturated aqueous sodium bicarbonate and water, dried (MgSO<sub>4</sub>), and evaporated under vacuum to give a liquid (7.42 g) which was chromatographed on silica gel (300 g). Elution with a mixture of ether and hexane (2:8 by volume) gave the required propenoic acid benzyl ester as a colourless liquid (7.13 g, 92%). Found: C, 70.69; H, 7.42. C<sub>13</sub>H<sub>16</sub>O<sub>3</sub> requires C, 70.89; H, 7.32%.

#### EXAMPLES 2 - 4

The following compounds were prepared by the general procedure of Example 1 using propyliodide, 2-vinylpyridine or t-butyl acrylate respectively as starting material instead of 2-methoxyethyl-bromide.



Example No.	R <sup>5</sup>	Analysis % (Theoretical in brackets)		
		C	H	N
2	$\text{CH}_3(\text{CH}_2)_2^-$	76.37 (76.44)	8.01 (7.90)	
3	 $(\text{CH}_2)_2^-$	75.95 (76.38)	6.41 (6.41)	5.20 (5.24)
4	$(\text{CH}_3)_3\text{CO}_2\text{C}(\text{CH}_2)_2^-$	70.48 (70.32)	7.72 (7.64)	

**EXAMPLE 5**2-(2-Methylthioethyl)propenoic acid benzyl ester

Sodium hydride (0.96 g, 50% suspension in mineral oil) was added to a stirred solution of t-butyl benzyl malonate (5 g) in dry dimethylformamide (50 ml), maintained at 0 °C under an atmosphere of nitrogen. After stirring for 15 minutes, 2-chloroethyl-methyl sulphide (2.21 g) in dimethylformamide (10 ml) was added dropwise, while the temperature of the reaction was maintained below 10 °C. The reaction was allowed to warm to room temperature and stirred for 15 hours when water was cautiously added. The reaction mixture was extracted with ethyl acetate (2 x 100 ml), the ethyl acetate extracts were washed with water (4x), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give 4-methylthio-2-t-butyloxycarbonyl-butanoic acid benzyl ester as an oil (6.4 g). This product was dissolved in trifluoroacetic acid (50 ml) with vigorous stirring at 0 °C under nitrogen. After stirring for 45 minutes, the trifluoroacetic acid was evaporated under reduced pressure at below 35 °C. Final traces of trifluoroacetic acid were removed by azeotrope with carbon tetrachloride (3 x 20 ml), to leave an oily residue, which was dissolved in pyridine (20 ml). To this solution were added piperidine (0.44 ml) and paraformaldehyde (1.47 g), and the mixture heated at 60 °C under nitrogen for 2 hours. The reaction mixture was cautiously poured onto iced water, and the pH adjusted to 1 using concentrated sulphuric acid. The mixture was extracted with ether (2 x 100 ml), and the ether extracts dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to yield the crude product (5.4 g) as an oil. This was chromatographed over silica gel, eluting with a mixture of hexane and ethyl acetate, to yield the title ester as a colourless oil (1.22 g). Found: C,64.69; H,6.55. C<sub>13</sub>H<sub>16</sub>O<sub>2</sub>S (0.25 H<sub>2</sub>O) requires C,64.85; H,6.91%.

**EXAMPLE 6**2-(2-Phenethyl)propenoic acid benzyl ester

Titanium tetraethoxide (7.72 g, 33.8 mmole), rinsed in with benzyl alcohol (50 ml) was added under nitrogen to a solution of 2-(2-phenylethyl)propenoic acid ethyl ester (20.23 g, 99 mmole) in benzyl alcohol (400 ml). The resulting solution was stirred at 100 °C under nitrogen for 18 hours, cooled to room temperature, and acidified with 1N hydrochloric acid (140 ml). The mixture was then extracted with a mixture of ether and hexane (1:1 by volume). Washing the organic extract with saturated aqueous sodium bicarbonate caused a thick precipitate to form in the aqueous phase, which when separated was re-extracted with ether/hexane. The combined organic extracts were washed with saturated sodium chloride

solution, dried ( $\text{MgSO}_4$ ), and the solvent evaporated under vacuum. Distillation of excess benzyl alcohol ( $63^\circ\text{C}$ , 2 torr) gave the crude product as a brown oil. Chromatography on silica gel (600 g), eluting with hexane containing increasing proportions of methylene chloride (2:8 to 4:6 by volume) gave the required ester (19.04 g, 72%) which was used without further purification.

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**EXAMPLE 7**2-[2-(1-Oxoisoindolinyl)methyl]propenoic acid t-butyl ester

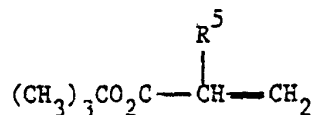
A solution of isoindolinone (2.13 g, 16 mmole) in dimethylformamide (20 ml) was added to a stirred suspension of 80% sodium hydride (0.53 g, 17.6 mmole) in dry dimethylformamide (20 ml) under nitrogen at room temperature. After 2 hours the orange suspension was cooled to  $0^\circ\text{C}$  and a solution of t-butyl 2-bromomethylpropenate (3.52 g, 16 mmole) in dry dimethylformamide (5 ml) was added slowly. After 0.5 hours at  $0^\circ\text{C}$  the reaction mixture was poured into diethyl ether and the solution washed with water (4x), dilute hydrochloric acid (2x) and dilute aqueous sodium hydrogen carbonate (2x). After drying ( $\text{Na}_2\text{SO}_4$ ),  
 15 evaporation of the solvent under vacuum yielded a yellow oil (3.0 g). Chromatography on silica eluting with dichloromethane/hexane and dichloromethane/diethyl ether mixtures gave the pure title propenate as a colourless oil (2.06 g, 47%). Found: C,70.12; H,7.10; N,5.03.  $\text{C}_{16}\text{H}_{19}\text{NO}_3$  requires C,70.31; H,7.01; N,5.12%.

EXAMPLE 8 - 11

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The following compounds were prepared following the procedure of Example 7 using appropriate amine starting materials and using potassium carbonate as the base and acetonitrile as the solvent instead of sodium hydride and dimethylformamide respectively.

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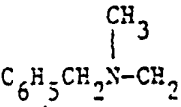
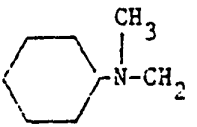
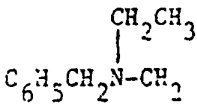
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5	Example	$R^5$	Analysis % (Theoretical in brackets) or Thin layer chromatography C      H      N		
10	8		Rf 0.5		
			(silica; Et <sub>2</sub> O, CH <sub>2</sub> Cl <sub>2</sub> , 1:9)		
15	9		Rf 0.65		
			(silica; Et <sub>2</sub> O)		
20	10		74.41	9.39	5.38
			(74.14	9.15	5.09)

30

35	Example	$R^5$	Analysis % (Theoretical in brackets) C      H      N		
40	11	$(C_6H_5CH_2)_2N-CH_2$	78.09	8.20	4.18
			(78.30	8.06	4.15)

45

**EXAMPLE 12**2-(Benzyloxycarbonylmethyl)propenoic acid t-butyl ester

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To a stirred solution of 2-(benzyloxycarbonylmethyl)propenoic acid (25.0 g, 114.0 mmole) in dichloromethane (200 ml) at -78° C was added condensed isobutylene (50 ml) and concentrated sulphuric acid (1 ml). The mixture was allowed to warm to room temperature and kept for 72 hours. After this time the solution was washed with 10% sodium carbonate solution (3 x 200 ml), dried over magnesium sulphate and  
 55 evaporated to give the required ester as a pale yellow oil (29.4 g, 90%). Found: C,69.60; H,7.35. C<sub>16</sub>H<sub>20</sub>O<sub>4</sub> requires: C,69.55; H,7.30%.

**EXAMPLE 13**

2-(t-Butoxycarbonylamino)propenoic acid benzyl ester

1,1'-Carbonyldiimidazole (8.10 g, 50 mmole) was added in small portions to a stirred solution of t-butoxycarbonylserine benzyl ester (14.75 g, 50 mmole) and triethylamine (5.05 g, 50 mmole) in dry tetrahydrofuran (100 ml) at room temperature. After stirring at room temperature for 16 hours, the reaction mixture was poured into diethyl ether, the organic phase washed sequentially with dilute hydrochloric acid, water and aqueous sodium carbonate, dried over sodium sulphate and evaporated under vacuum to give an oil (14 g). Chromatography on silica eluting with a mixture of hexane and dichloromethane gave the title propenoate as a yellow oil (10.98 g, 79%). Rf 0.5 (silica; dichloromethane, hexane 1:1).

## EXAMPLE 14

2-(Benzyloxycarbonylamino)propenoic acid t-butyl ester

The title compound was obtained via N-benzyloxycarbonyl-O-benzyl-L-serine t-butyl ester which was prepared by a different route to that described in the literature (Recl. Trav. Chim. Pays-Bas, 1964, 83, 99). To a stirred solution of O-benzyl-L-serine (25.0 g, 128 mmole) in water (200 ml) and dioxane (100 ml) was added sodium carbonate (7.46 g, 70 mmole) at room temperature. A solution of dibenzylidicarbonate (36.1 g, 126 mmole) in dioxane (100 ml) was added dropwise and the mixture stirred for 18 hours. Dioxane was evaporated under vacuum and the aqueous residue extracted with diethyl ether. Evaporation of the dried (Na<sub>2</sub>SO<sub>4</sub>) extracts under vacuum gave a white solid which was washed with hexane to yield crude N-benzyloxycarbonyl-O-benzyl-L-serine (39.57 g, 95%). This material was treated with isobutylene (360 ml) and concentrated sulphuric acid (2 ml) in dichloromethane. The reaction mixture was shaken at room temperature in a pressure vessel for 3 days. The mixture was washed with dilute sodium hydrogen carbonate and the dichloromethane evaporated. The residue was dissolved in diethyl ether, washed with dilute sodium hydrogen carbonate, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under vacuum. Purification by column chromatography on silica eluting with diethyl ether-dichloromethane mixtures gave N-benzyloxycarbonyl-O-benzyl-L-serine t-butyl ester (36.66 g, 79%) as an oil. Found: C,68.90; H,7.06; N,3.46. C<sub>22</sub>H<sub>27</sub>NO<sub>5</sub> requires C,68.55; H,7.06; N,3.63%.

The above compound (36.06 g, 94 mmole) was dissolved in dry t-butanol (500 ml) and treated with potassium t-butoxide (12.59 g, 112 mmole) at room temperature under nitrogen. After 2 hours, the reaction mixture was poured into 2N hydrochloric acid (50 ml) and water (350 ml) and extracted with diethyl ether. The extract was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated under vacuum. The residue was purified by column chromatography on silica eluting with dichloromethane-hexane mixtures to yield the title compound as an oil (22.50 g, 80%). Rf. 0.65 (silica; 50% diethyl ether-hexane). Elemental analysis was precluded by polymerisation at room temperature. The product was stored below 0 °C.

## EXAMPLE 15

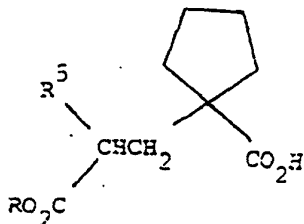
3-(1-Carboxycyclopentyl)-2-(2-methoxyethyl)propanoic acid benzyl ester

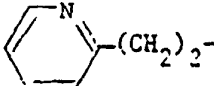
n-Butyl lithium (2.5 M in hexane, 18.16 ml, 45.4 mmole) was added dropwise under nitrogen to a stirred solution of diisopropylamine (4.59, 45.4 mmole) in dry tetrahydrofuran (20 ml) keeping the temperature between -40 ° and -20 °C. Stirring was continued at -20 °C for half an hour and cyclopentane carboxylic acid (2.59 g, 22.7 mmole) in dry tetrahydrofuran (10 ml) was added over five minutes, keeping the temperature at -20 °C. The mixture was allowed to attain room temperature over one and a half hours, stirred for a further one hour and then cooled to -73 °C. 2-(2-Methoxyethyl)propenoic acid benzyl ester (5.0 g, 22.7 mmole) in dry tetrahydrofuran (10 ml) was added dropwise keeping the temperature below -70 °C. After two hours at -77 °C, the mixture was quickly warmed to 0 °C, acidified with 5N hydrochloric acid, and extracted with hexane. The hexane extract was washed (x 7) with a mixture of water and saturated aqueous sodium bicarbonate (1:1 by volume) to remove unreacted cyclopentane carboxylic acid. The extract was washed with water, dried (MgSO<sub>4</sub>) and evaporated under vacuum to give a pale yellow oil (6.3 g) which was chromatographed on silica gel (600 g). Gradient elution starting with a mixture of ethyl acetate and hexane (3:7 by volume) changing to neat ethyl acetate gave the required product as a colourless oil (4.0 g, 53%). Found: C,68.39; H,7.99. C<sub>19</sub>H<sub>26</sub>O<sub>5</sub> requires C,68.24; H,7.84%. On prolonged standing the material solidified and when recrystallised from hexane gave a white solid, m.p. 41-2 °C.

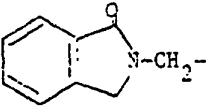
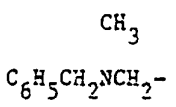
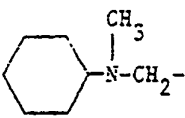
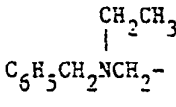
EXAMPLES 16 - 28

The following compounds were prepared by the procedure of Example 15 using as starting material the

appropriate propenoic acid ester of Example 2 to 14. Apart from Examples 16 and 17 the products were obtained as oils. Examples 24 and 25 were isolated as hydrochloride salts. Two molar equivalents of dithiocyclopentane carboxylic acid dianion were used in the preparation of Examples 20 and 28.



Example No.	R	R <sup>5</sup>	Analysis % (Theoretical in brackets)		
			C	H	N
16	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> -	71.93 (71.67)	8.09 (8.23)	- -
17	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub> -	75.77 (75.76)	7.49 (7.42)	- -
18	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -		Rf 0.2 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> CH <sub>3</sub> CO <sub>2</sub> H, 10:90:1)		
19	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	(CH <sub>3</sub> ) <sub>3</sub> CO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> -	Rf 0.7 (silica; Et <sub>2</sub> O)		
20	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	(CH <sub>3</sub> ) <sub>3</sub> CO <sub>2</sub> CNH-	64.40 (64.43)	7.67 (7.47)	3.55 (3.58)

Example No.	R	R <sup>5</sup>	Analysis % (Theoretical in brackets)		
			C	H	N
21	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> S(CH <sub>2</sub> ) <sub>2</sub> -	64.88 (65.12)	7.29 (7.48)	-
22	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O <sub>2</sub> CCH <sub>2</sub> -	67.52 (67.67)	7.88 (7.74)	-
23	(CH <sub>3</sub> ) <sub>3</sub> C-		Rf 0.3 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> , 1:9)		
24	(CH <sub>3</sub> ) <sub>3</sub> C-		Rf 0.5 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> , 1:9)		
25	(CH <sub>3</sub> ) <sub>3</sub> C-		Rf 0.5 (silica, CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> , 1:9)		
26	(CH <sub>3</sub> ) <sub>3</sub> C-		69.76 (69.70)	9.06 (8.91)	3.55 (3.52) <sup>(1)</sup>
27	(CH <sub>3</sub> ) <sub>3</sub> C-	(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> NCH <sub>2</sub> -	74.38 (74.47)	8.41 (8.26)	2.91 (3.10)
28	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> OCONH-	64.33 (64.43)	7.71 (7.47)	3.29 (3.58)

(1) Solvate with 0.1 CH<sub>2</sub>Cl<sub>2</sub>.

#### EXAMPLES 29-34

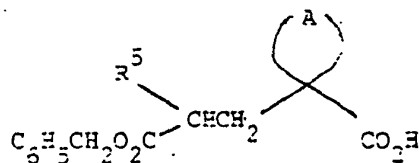
The following compounds were prepared following the procedure of Example 15 but using as starting materials the appropriate cycloalkane or cycloalkene carboxylic acid instead of cyclopentane carboxylic



acid, and reacting the anion with 2-propylpropenoic acid benzyl ester or 2-(2-methoxyethyl)propenoic acid benzyl ester as appropriate.

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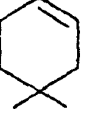
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<div>5</div> <div>Example</div> <div>No.</div> <div>10</div>	<div>R</div>	<div>A</div> <div></div>	<div>Analysis %</div> <div>(Theoretical in brackets)</div> <div>C      H</div>
<div>15</div> <div>29</div>	$\text{CH}_3(\text{CH}_2)_2^-$	<div></div>	<div>72.27    7.76</div> <div>(72.12    7.65)</div>
<div>25</div> <div>30</div> <div>30</div>	$\text{CH}_3\text{O}(\text{CH}_2)_2^-$	<div></div>	<div>68.22    7.31</div> <div>(68.65    7.28)</div>
<div>35</div> <div>31</div> <div>40</div>	$\text{CH}_3\text{O}(\text{CH}_2)_2^-$	<div></div>	<div>69.10    8.44</div> <div>(68.94    8.10)</div>
<div>45</div> <div>32</div> <div>50</div>	$\text{CH}_3\text{O}(\text{CH}_2)_2^-$	<div></div>	<div>69.03    7.85</div> <div>(69.34    7.57)</div>

5	Example	R	A	Analysis %
	No.			(Theoretical in brackets)
10			C      H	
15	33	$\text{CH}_3\text{O}(\text{CH}_2)_2^-$		68.95    8.38
20				(68.94    8.10)
25	34	$\text{CH}_3\text{O}(\text{CH}_2)_2^-$		71.48    6.75
30				(72.23    6.85)
35				

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**EXAMPLE 35**3-(1-Carboxycyclopentyl)propanoic acid t-butyl ester

45 To a stirred solution of lithium diisopropylamide (0.43 mole in dry tetrahydrofuran (300 ml) at  $-20^\circ\text{C}$  under nitrogen atmosphere was added cyclopentane carboxylic acid (22.7 g; 0.20 mole). The solution was allowed to warm to room temperature and after 2 hours was cooled to  $-10^\circ\text{C}$  and added by cannula to a stirred solution of t-butyl 3-bromopropionate (44.4 g, 0.21 mole) in tetrahydrofuran (100 ml). The resulting solution was allowed to warm to room temperature and kept overnight. Hydrochloric acid (3N, 250 ml) was

50 cautiously added, followed by diethyl ether (500 ml) and the layers allowed to separate. The aqueous layer was washed with diethyl ether (300 ml) and the ether layers were combined, washed with water (300 ml), dried over magnesium sulphate and evaporated to give an oil. The oil was taken up in diethyl ether (300 ml) and washed with saturated sodium hydrogen carbonate solution (3 x 100 ml) until no further cyclopentane carboxylic acid remained. The diethyl ether solution was then extracted with 10% sodium

55 carbonate solution, (4 x 150 ml), the aqueous phase separated, acidified with 2N hydrochloric acid, and extracted with diethyl ether (3 x 200 ml). The diethyl ether layer was separated, washed with water (300 ml), dried over magnesium sulphate and evaporated to give an oil that readily crystallised. Recrystallisation from pentane gave a colourless solid (10.4 g, 21%) m.p.  $78-81^\circ\text{C}$  (from pentane). Found: C, 64.70; H, 9.18.

$C_{13}H_{22}O_4$  requires: C,64.44; H,9.15%.

#### EXAMPLE 36

- 5 3-(1-Carboxycyclopentyl)propanoic acid ethyl ester was prepared following the procedure of Example 35 starting with ethyl 3-bromopropionate. Found: C,61.91; H,8.53.  $C_{11}H_{18}O_4$  requires C,61.66; H,8.47%.

#### EXAMPLE 37

- 10 3-(1-Carboxycyclopentyl)propanoic acid benzyl ester was prepared from benzyl 3-bromopropionate following the procedure of Example 35 to give the benzyl ester as an oil. Found: C,69.76; H,7.18.  $C_{15}H_{20}O_4$  requires C,69.55; H,7.29%.

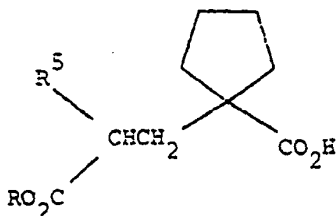
#### EXAMPLE 38

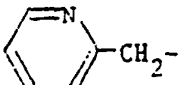
- 15 3-(1-Carboxycyclopentyl)-2-(methoxymethyl)propanoic acid t-butyl ester

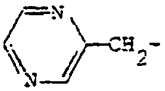
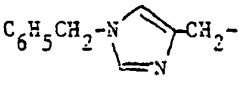
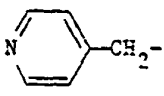
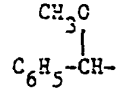
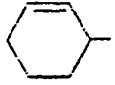
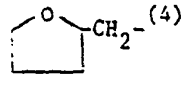
A solution of t-butyl 3-(1-carboxycyclopentyl)propanoate (1.0 g, 4.13 mmole) in dry tetrahydrofuran was added to a stirred solution of lithium diisopropylamide (9.29 mmole) in dry tetrahydrofuran (50 ml) at  $-78^{\circ}C$  under nitrogen. After 0.5 hours, chloromethyl methyl ether (0.53 g, 6.58 mmole) was added and the mixture  
 20 was allowed to warm to room temperature over 16 hours. The solution was poured into water, acidified to pH 3 with 2N hydrochloric acid and extracted with ethyl acetate (3 x 50 ml). The organic layer was separated, dried over magnesium sulphate and evaporated to give a colourless oil that was chromatographed on silica gel eluting with a mixture of diethyl ether and dichloromethane (1:9 - 1:4 by volume). Evaporation of the appropriate fractions gave the title compounds as a colourless oil (0.78 g, 66%). Found:  
 25 C,62.75; H,8.94.  $C_{15}H_{26}O_5$  requires: C,62.91; H,9.15%.

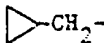



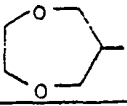
#### EXAMPLES 39-69

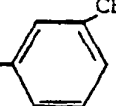

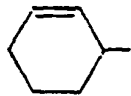
- The following compounds were prepared by the procedure of Example 38 using as starting materials  
 30 the appropriate propanoic ester of Example 35, 36 or 37 and the appropriate chloro, bromo, iodo or trifluoromethanesulphonyloxy derivative of formula  $R^5X$ . Example 50 was obtained as a solid (m.p.  $94-6^{\circ}C$ ), the other products were oils.



Example No.	R	R <sup>5</sup>	Analysis % (Theoretical in brackets) C      H      N		
39	(CH <sub>3</sub> ) <sub>3</sub> C-		62.38 (61.94)	7.40 (7.72)	3.47 3.42 <sup>(1)</sup>
40	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>3</sub> -	Rf 0.45 (silica, Et <sub>2</sub> O, hexane, 2:1)		
41	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>2</sub> H <sub>5</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	64.94 (64.94)	9.55 (9.62)	- -
42	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> -	61.86 (61.79)	9.15 (9.15)	- -

Example No.	R	R <sup>5</sup>	Analysis % (Theoretical in brackets)		
			C	H	N
43	(CH <sub>3</sub> ) <sub>3</sub> C-		64.35 (64.65)	8.06 7.84	8.14 8.38)
44	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>2</sub> =CH-CH <sub>2</sub> -	67.72 (68.05)	9.47 9.28)	-
45	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -N 	69.28 (69.87)	7.58 7.82	6.55 6.79)
46	(CH <sub>3</sub> ) <sub>3</sub> C-		67.52 (67.53)	8.01 8.20	4.24 4.15) (2)
47	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> -C≡C-CH <sub>2</sub> -	68.70 (69.36)	8.78 8.90)	-
48	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O-(CH <sub>2</sub> ) <sub>4</sub> -	R <sub>f</sub> 0.85 (silica; Et <sub>2</sub> O, CH <sub>2</sub> Cl <sub>2</sub> 1:4)		
49	(CH <sub>3</sub> ) <sub>3</sub> C-	Br-(CH <sub>2</sub> ) <sub>4</sub> -	55.35 (55.07)	7.87 8.27)	-(3)
50	(CH <sub>3</sub> ) <sub>3</sub> C-		69.90 (69.59)	8.41 8.34)	-
51	(CH <sub>3</sub> ) <sub>3</sub> C-		70.55 (70.77)	9.44 9.38)	-
52	(CH <sub>3</sub> ) <sub>3</sub> C-		R <sub>f</sub> 0.4 (silica; Et <sub>2</sub> O, CH <sub>2</sub> Cl <sub>2</sub> 1:2)		

Example No.	R	R <sup>5</sup>	Analysis % (Theoretical in brackets)		
			C	H	N
53	C <sub>2</sub> H <sub>5</sub> -	CH <sub>3</sub> CCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> -	Rf 0.15 (silica; Et <sub>2</sub> O, hexane 1:1)		
54	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> -	65.40 (65.60)	9.51 (9.44)	- -
55	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> CH <sub>2</sub> CO-	64.22 (64.41)	8.94 (8.78)	- -
56	C <sub>2</sub> H <sub>5</sub> -	CH <sub>2</sub> =CHCH <sub>2</sub> -	65.91 (66.11)	8.60 (8.72)	- -
57	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> CH=CHCH <sub>2</sub> -	67.70 (67.85)	9.44 (9.54)	(2)
58	(CH <sub>3</sub> ) <sub>3</sub> C-	 -CH <sub>2</sub> -	Rf 0.91 (silica; ethylacetate, toluene, 1:1)		
59	(CH <sub>3</sub> ) <sub>3</sub> C-		69.32 (69.64)	9.47 (9.74)	
60	(CH <sub>3</sub> ) <sub>3</sub> C-		65.42 (65.36)	8.49 (9.03)	
61	(CH <sub>3</sub> ) <sub>3</sub> C-		66.03 (65.36)	9.11 (9.03)	
62	(CH <sub>3</sub> ) <sub>3</sub> C-		62.01 (62.05)	8.77 (8.87)	(5)
63	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> OCH <sub>2</sub> CH-   CH <sub>3</sub>	62.83 (63.28)	9.42 (9.38)	(6)

Example No.	R	R <sup>S</sup>	Analysis % (Theoretical in brackets)		
			C	H	N
64	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	7.19 (7.26)	8.68 (8.41)	
65	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O-  CH <sub>2</sub> -	73.34 (73.57)	7.97 (7.83)	(7)
66	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O <sub>2</sub> C-  CH <sub>2</sub> -	Rf 0.61 (silica; Et <sub>2</sub> O, CH <sub>2</sub> Cl <sub>2</sub> , 1:4)		
67	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> C≡C-CH <sub>2</sub> -	70.75 (70.85)	3.03 (3.30)	(8)
68	CH <sub>3</sub> CH <sub>2</sub> -	CH <sub>3</sub> C≡C-CH <sub>2</sub> -	66.69 (67.64)	8.79 (8.32)	
69	CH <sub>3</sub> CH <sub>2</sub> -		69.28 (69.36)	9.05 (8.90)	

- (1) Solvate with CH<sub>3</sub>CO<sub>2</sub>H, 0.2 CH<sub>2</sub>Cl<sub>2</sub>
- (2) 0.25 H<sub>2</sub>O
- (3) Solvate with 0.5 C<sub>4</sub>H<sub>10</sub>O
- (4) Using 2-trifluoromethylsulphonyloxymethyl-2,3,4,5-tetrahydrofuran
- (5) 0.33 H<sub>2</sub>O
- (6) Solvate with 0.125 CH<sub>2</sub>Cl<sub>2</sub>
- (7) 0.125 H<sub>2</sub>O
- (8) Hemihydrate

**EXAMPLE 70**  
cis-5-Amino-cis-2-ethyl-r-1-cyclohexanecarboxylic acid methyl ester hydrochloride

5-Amino-2-ethylbenzoic acid (7.0 g, 42.37 mmole) was dissolved in hot ethanol (120 ml) and water (200



ml) and hydrogenated at 45 °C and 50 psi (3.45 bar) pressure over platinum (from PtO<sub>2</sub>, 1.0 g) for two days. Further amounts of catalyst (1.0 g) were added after seven and twenty four hours. Filtration through avicel and evaporation under vacuum gave a white solid which was dissolved in water and taken up on cation exchange resin (Dow AG 50 W-X8). Elution with 0.5% aqueous pyridine, and evaporation under vacuum gave the crude amino acid as a white solid (5.81 g). Trituration with hot acetone to remove a small amount of starting material, followed by recrystallisation from a mixture of acetone and water and then from acetonitrile and water gave cis-5-amino-cis-2-ethyl-r-1-cyclohexanecarboxylic acid (3.4 g) as a high melting white solid. Found: C,63.02; H, 10.28, N, 8.13. C<sub>9</sub>H<sub>17</sub>NO<sub>2</sub> requires C,63.13; H,10.00; N,8.18%.

An ice cold suspension of the above acid (3.35 g, 19.56 mmole) in methanol (100 ml) was stirred and saturated with hydrogen chloride and the resulting solution allowed to stand at room temperature overnight. Evaporation of the solvent under vacuum followed by trituration of the residue with diethyl ether and recrystallisation from a mixture of diethyl ether and methanol gave the required methyl ester hydrochloride as fine white crystals. (3.57 g, 82%). m.p. 200-201 °C. Found: C,53.86; H,9.05; N,6.14. C<sub>10</sub>H<sub>19</sub>NO<sub>2</sub>.HCl requires C,54.17; H,9.09; N,6.32%.

#### EXAMPLE 71

cis-3-Amino-cis-5-methyl-r-1-cyclohexanecarboxylic acid methyl ester hydrochloride

3-Amino-5-methylbenzoic acid (7.2 g, 47.6 mmole) was hydrogenated and worked-up as described in Example 70, to give the cyclohexane carboxylic acid (3.30 g; 44%) as a high melting white solid. Found: C,60.81; H,9.67; N,8.80%. C<sub>8</sub>H<sub>15</sub>NO<sub>2</sub> requires: C,61.12; H,9.62; N,8.91%. Esterification of the acid (3.17 g, 20.16 mmole) with hydrogen chloride in methanol as previously described gave the methyl ester hydrochloride as a white solid (3.35 g, 80%). m.p. 172.5-173.5 °C. Found: C,52.36; H,8.63; N,6.62. C<sub>9</sub>H<sub>17</sub>NO<sub>2</sub>.HCl requires C,52.04; H,8.73; N,6.74%.

#### EXAMPLE 72

cis-3-Amino-cis-5-methyl-r-1-cyclohexanecarboxylic acid ethyl ester hydrochloride

Esterification of cis-3-amino-cis-5-methyl-r-1-cyclohexane carboxylic acid (2.0 g) with ethanol and hydrogen chloride gave the ethyl ester hydrochloride (1.4 g, 75%). Found: C,51.23; H,8.52; N,7.13. C<sub>10</sub>H<sub>20</sub>NO<sub>2</sub>.HCl requires C,54.17; H,9.09; N,6.32%.

#### EXAMPLE 73

cis-3-Amino-cis-4-ethyl-r-1-cyclohexanecarboxylic acid methyl ester hydrochloride

3-Amino-4-ethyl benzoic acid (14.0 g, 84.7 mmole) was hydrogenated and worked-up as described in Example 70, to give the cyclohexane carboxylic acid (6.36 g 43%) as a light fibrous white solid. m.p. >250 °C. Found: C,61.83; H,9.80; N,8.13. C<sub>9</sub>H<sub>17</sub>NO<sub>2</sub>. 0.2 H<sub>2</sub>O requires C,61.82; H,10.03; N,8.01%. Esterification of the above acid (6.0 g, 35.04 mmole) as described in Example 70 gave the methyl ester hydrochloride as a white solid (7.02 g, 90%). m.p. 161.5-162 °C. Found: C,53.79; H,9.13; N,6.33. C<sub>10</sub>H<sub>19</sub>NO<sub>2</sub>.HCl requires C,54.17; H,9.09; N,6.32%.

#### EXAMPLE 74

cis-3-Amino-cis-4-ethyl-r-1-cyclohexanecarboxylic acid methyl ester hydrochloride

Esterification of cis-3-amino-cis-4-ethyl-r-1-cyclohexane carboxylic acid (2.5 g) with ethanol and hydrogen chloride gave the ethyl ester hydrochloride (2.0 g, 75%). Found: C,54.31; H,9.53; N,5.92. C<sub>11</sub>H<sub>22</sub>NO<sub>2</sub>.HCl requires C,56.04; H,9.41; N,5.94%.

#### EXAMPLE 75

cis-3-Amino-cis-4-methyl-r-1-cyclohexanecarboxylic acid methyl ester hydrochloride

3-Amino-4-methylbenzoic acid (3.2 g, 21.2 mmole) was hydrogenated and worked-up as described in Example 42, but without cation exchange chromatography, to give the cyclohexane carboxylic acid (1.31 g, 39%) as a white solid, m.p. 258-261 °C (decomp.). Found: C,61.03; H,9.89; N,8.90. C<sub>8</sub>H<sub>15</sub>NO<sub>2</sub> requires: C,61.11; H,9.52; N,8.91%. Esterification as described in Example 42, gave the methyl ester hydrochloride as a hygroscopic foam (1.31 g, 87%). Found: C,51.84; H,8.99; N,6.73. C<sub>9</sub>H<sub>17</sub>NO<sub>2</sub>.HCl requires C,52.03; H,8.73; N,6.74%.

**EXAMPLE 76**cis-3-Aminocyclohexanecarboxylic acid ethyl ester hydrochloride

cis-3-Aminocyclohexanecarboxylic acid hydrochloride (5.25 g, 36.7 mmole) was esterified with ethanol  
 5 and hydrogen chloride, as previously described, to give the ethyl ester hydrochloride as a white solid (6.62 g, 87%). m.p. 163-4 ° C. Found: C,51.94; H,8.73; N,6.47. C<sub>9</sub>H<sub>17</sub>NO<sub>2</sub>HCl requires C,52.03; H,8.83; N,6.74%.

**EXAMPLE 77**cis-3-Aminocyclohexanecarboxylic acid benzyl ester para-toluene sulphonate

10 cis-3-Aminocyclohexanecarboxylic acid hydrochloride (8.78 g, 49 mmole) was refluxed for 24 hours with benzyl alcohol (26.4 g, 0.24 mole) and para-toluenesulphonic acid monohydrate (11.17 g, 0.59 mole) in toluene (150 ml) using a Dean-Stark trap. On cooling and addition of diethyl ether the required benzyl ester crystallised as a white solid (18.68 g, 94%), m.p. 148-150 ° C. Found: C,62.21; H,6.75; N,3.34. C<sub>21</sub>H<sub>27</sub>NO<sub>5</sub>S  
 15 requires C,62.20; H,6.71; N,3.45%.

**EXAMPLE 78**cis-4-Aminocyclohexanecarboxylic acid benzyl ester para-toluene sulphonate

20 This ester was prepared from cis-4-aminocyclohexane carboxylic acid hydrochloride following the procedure described in Example 77 and was obtained in 97% yield as a white solid, m.p. 172-4 ° C. Found: C,62.21; H,6.62; N,3.33. C<sub>21</sub>H<sub>27</sub>NO<sub>5</sub>S requires C,62.20; H,6.71; N,3.45%.

**EXAMPLE 79**trans-3-Amino-1-propyl-r-1-cyclopentanecarboxylic acid methyl ester

(a) 3-Cyclopentenecarboxylic acid (7.5 g, 66.9 mmole) in dry tetrahydrofuran (15 ml) was added dropwise under nitrogen to a stirred solution of lithium diisopropylamide prepared from diisopropylamine (19.7 ml, 0.14 mole) and 2.5 M n-butyl lithium in hexane (56.2 ml, 0.14 mole) in dry tetrahydrofuran (150 ml) at -60 ° C. The resulting suspension was allowed to warm to room temperature and then stirred for a  
 30 further hour, by which time a clear solution was obtained. Iodopropane (7.18 ml, 83.6 mmole) was added dropwise at -60 ° C, and the mixture was once again allowed to warm to room temperature and then stirred overnight. The solution was cooled to 15 ° C, water (10 ml) was added followed by 2N hydrochloric acid to pH 3. The organic layer was separated and the aqueous phased extracted twice with methylene  
 35 chloride. The combined organic extracts were washed with saturated salt solution, dried (MgSO<sub>4</sub>) and evaporated under vacuum to give a crude product which was chromatographed on silica gel (200 g), eluting with a mixture of ethyl acetate and hexane to give 1-propyl-3-cyclopentene-carboxylic acid (7.96 g, 77%) as a hygroscopic solid.

(b) Bromine (7.28 g, 45 mmole) in carbon tetrachloride (20 ml) was added dropwise at 6-10 ° C to a stirred solution of the above product (6.39 g, 41 mmole) in carbon tetrachloride (30 ml). After half an hour the solvent was evaporated under vacuum and the residual dibromo derivative refluxed for one and a quarter hours with potassium carbonate (6.8 g, 49 mmole) in methylethylketone (500 ml). The mixture was filtered, evaporated to a small volume, and residue taken up in ether. Washing with water, drying (MgSO<sub>4</sub>) and evaporation gave an oil which was chromatographed on silica gel (120 g). Gradient elution  
 45 with increasing proportions of ethyl acetate in hexane (35:75 to 60:40 by volume) gave 6-endo-bromo-4-propyl-2-oxabicyclo[2,2,1]heptan-3-one as a pale orange oil (8.79 g, 91%).

(c) The bromo-lactone from step (b), (4.0 g, 17.2 mmole) in absolute ethanol (35 ml) was hydrogenated at 50 psi (3.45 bar) over magnesium oxide (6.92 g, 0.172 mole) and 10% palladium on charcoal (800 mg). The reduction was continued for forty hours; more catalyst (1.0 g) being added after seven and twenty-four hours respectively. The mixture was filtered through avicel, the solvent evaporated under vacuum and the residue chromatographed on silica gel (150 g), eluting with increasing proportions of  
 50 ether in hexane to give 4-propyl-2-oxabicyclo[2,2,1]heptan-3-one as a colourless oil (1.13 g; 42%).

(d) The lactone from step (c) (1.13 g, 7.28 mmole) was refluxed in methanol (30 ml) containing concentrated sulphuric acid (0.15 ml) for one and a quarter hours. The mixture was evaporated to a small  
 55 volume and the residue partitioned between ether and water. The organic phase was washed with water, dried over magnesium sulphate and evaporated under reduced pressure to give cis-3-hydroxy-1-propyl-r-1-cyclopentanecarboxylic acid methyl ester as a colourless oil (0.94 g, 70%).

(e) para-Toluenesulphonylchloride (1.43 g, 7.5 mmole) was added portion-wise to an ice cold solution of

the hydroxy ester from step (d) (930 mg, 5 mmole) in pyridine (10 ml). The mixture was allowed to warm gradually to room temperature overnight, and after eighteen hours, poured onto iced water. The mixture was extracted with ether, the organic extract being washed sequentially with 1N hydrochloric acid, water, saturated sodium bicarbonate and water. Drying ( $\text{MgSO}_4$ ) and evaporation under vacuum gave an oil which was chromatographed on silica gel (80 g) eluting with a mixture of ethyl acetate and hexane to give the required 3-para-toluenesulphonyl derivative (1.5 g, 89%). This compound (1.45 g, 4.3 mmole) was refluxed for eighteen hours with sodium azide (1.11 g, 17 mmole) in methanol (20 ml) and water (10 ml). Most of the methanol was evaporated off under vacuum and the residue was extracted with methylene chloride. The organic extract was washed with water, dried ( $\text{MgSO}_4$ ) and evaporated under vacuum to give an oil which was chromatographed on silica gel (40 g). Gradient elution with a mixture of ethyl acetate and hexane give trans-3-azido-1-propyl-r-1-cyclopentanecarboxylic acid methyl ester as a colourless oil (0.79 g, 89%).

(f) The azide from step (e), (730 mg, 3.4 mmole) in methanol (25 ml) was hydrogenated for four hours at 50 psi pressure over 10% palladium on charcoal (80 mg). The mixture was filtered through a short Avicel column and evaporated under vacuum to give the required title amine (619 mg, 97%) as a pale yellow hygroscopic oil. Found: C,54.93; H,9.59; N,5.79%.  $\text{C}_{10}\text{H}_{19}\text{NO}_2 \cdot 2\text{H}_2\text{O}$  requires C,54.27; H,10.47; N,6.33%.

**EXAMPLE 80**

trans-3-Amino-cis-4-hydroxy-1-propyl-r-1-cyclopentanecarboxylic acid methyl ester

(a) 6-endo-Bromo-4-propyl-2-oxabicyclo[2,2,1]heptan-3-one from Example 48(b) (2.0 g, 8.6 mmole) was refluxed in methanol (30 ml) containing concentrated sulphuric acid (0.15 ml) for one and a quarter hours. The mixture was evaporated to a small volume and the residue was partitioned between ether and water. The organic extract was washed with water, dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to give cis-3-bromo-cis-4-hydroxy-1-propyl-r-1-cyclopentanecarboxylic acid methyl ester as an oil (2.18 g, 98%).

(b) The product from step (a) (2.14 g, 8.1 mmole) was refluxed with sodium azide (2.10 g, 32.3 mmole) in methanol (25 ml) and water (15 ml). After forty-eight hours a further amount of sodium azide (1.0 g) was added and reaction continued for four days. Most of the methanol was removed by evaporation under vacuum and the residue was extracted with methylene chloride. The extract was washed with water, dried ( $\text{MgSO}_4$ ) and evaporated under vacuum to give an oil which was chromatographed on silica gel (100 g). Gradient elution with increasing proportions of ethyl acetate in hexane gave trans-3-azido-cis-4-hydroxy-1-propyl-r-1-cyclopentanecarboxylic acid methyl ester as a colourless oil (1.24 g, 68%).

(c) The azide from step (b) was reduced as described in Example 50(f) to give the desired amino ester as an oil (1.06 g, 98%). Found: C,58.14; H,9.32; N,6.31.  $\text{C}_{10}\text{H}_{19}\text{NO}_3 \cdot 0.25 \text{H}_2\text{O}$  requires C,58.37; H,9.55; N,6.81%.

**EXAMPLE 81**

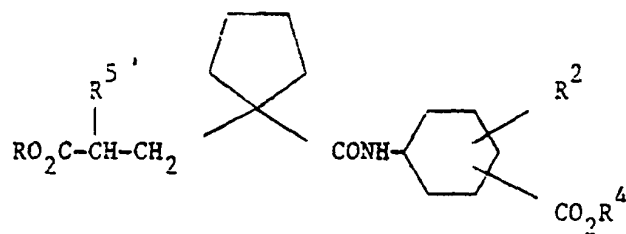
3-{1-[cis-4-Benzoyloxycarbonyl-cyclohexyl]carbamoyl}cyclopentyl}-2-(2-methoxyethyl)propanoic acid benzyl ester

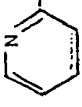
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.15 g, 6 mmole) was added to an ice cold stirred mixture of 3-(1-carboxycyclopentyl)-2-(2-methoxyethyl)propanoic acid benzyl ester (1.0 g, 3 mmole) cis-4-amino-cyclohexanecarboxylic acid benzyl ester p-toluenesulphonate (1.21 g, 3 mmole), 1-hydroxybenzotriazole (405 mg, 3mmole) and N-methylmorpholine (910 mg, 9 mmole) in dry methylene chloride (30 ml). After half an hour the mixture was allowed to attain room temperature and stirred for eighteen hours. The solvent was evaporated under vacuum and the residue partitioned between ether and water. The organic extract was washed sequentially with water, 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate, and water. Drying ( $\text{MgSO}_4$ ) and evaporation under vacuum gave an oil (1.6 g) which was chromatographed on silica gel (110 g) eluting with a mixture of ether and hexane (1:1 by volume) to give the required diester as a colourless oil (1.12 g, 67%). Found: C,72.07; H,8.00; N,2.52.  $\text{C}_{33}\text{H}_{43}\text{NO}_6$  requires C,72.10; H,7.89; N,2.55%.

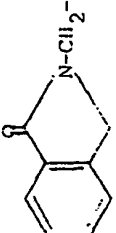
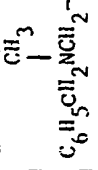
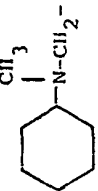
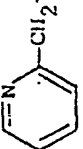
**EXAMPLES 82-159**

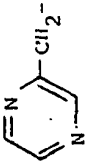
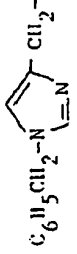
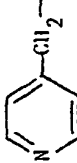
The following compounds of formula (V) wherein  $\text{R}^{13}$  and  $\text{R}^{14}$  are each  $\text{C}_1$ - $\text{C}_6$  alkyl or benzyl were prepared by the general procedure of Example 81 starting with the appropriate glutaric acid derivative of formula (III) from Examples 15-69 coupling with the appropriate amine of formula (IV). The products were

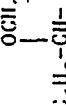
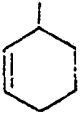
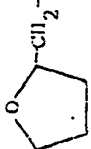
obtained as gums and oils. The stereochemistry of the cycloalkane substituents  $R^2$  and  $CO_2R^4$  is given with reference to the 1-carbamoyl substituent.



Example No.	R	R <sup>5</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
82	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> -	II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	74.21 8.16 2.80 (74.26 8.12 2.62)
83	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub> -	II	4-CO <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	73.20 7.69 2.60 (74.26 8.12 2.63)
84	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	 -(CH <sub>2</sub> ) <sub>2</sub> -	II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	74.53 7.74 4.83 (74.47 7.43 4.69)
85	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	(CH <sub>3</sub> ) <sub>3</sub> CO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> -	II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	71.72 7.95 2.38 (71.70 7.97 2.26)
86	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	(CH <sub>3</sub> ) <sub>3</sub> CO <sub>2</sub> CNH-	II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	68.23 7.71 4.59 (2) (68.27 7.69 4.55)
87	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> S(CH <sub>2</sub> ) <sub>2</sub> -	II	4-CO <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	66.24 8.24 3.22 (66.77 8.21 2.78)
88	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> OCCCH <sub>2</sub> -	II	4-CO <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	68.51 8.38 2.50 (68.48 8.34 2.58)


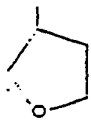
Example No.	R	R <sup>5</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
89	(CH <sub>3</sub> ) <sub>3</sub> C-		II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	RF 0.4 (silica; Et <sub>2</sub> O)
90	(CH <sub>3</sub> ) <sub>3</sub> C-		II	3-CO <sub>2</sub> C <sub>4</sub> H <sub>9</sub> (cis)	RF 0.8 (silica; Et <sub>2</sub> O, CH <sub>2</sub> Cl <sub>2</sub> 1:9)
91	(CH <sub>3</sub> ) <sub>3</sub> C-		II	3-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	RF 0.85 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> 1:9)
92	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> OCH <sub>2</sub> -	II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	69.56 8.78 2.82 (69.43 8.64 2.79)
93	(CH <sub>3</sub> ) <sub>3</sub> C-		II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	70.60 8.20 4.92 (3) (70.49 7.91 4.95)
94	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>3</sub> -	II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	70.32 9.02 2.56 (70.29 8.94 2.64)

Example No.	R	R <sup>5</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
95	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>2</sub> H <sub>5</sub> O(CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	70.22 8.93 2.69 (70.29 8.94 2.64)
96	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> <sup>-</sup>	II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	67.82 8.53 2.47 (68.23 8.68 2.57)
97	(CH <sub>3</sub> ) <sub>3</sub> C-		II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	68.51 7.85 7.66 (68.79 7.94 7.52)
98	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>2</sub> =CH-CH <sub>2</sub> <sup>-</sup>	II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	72.13 8.65 3.18 (72.40 8.71 2.81)
99	(CH <sub>3</sub> ) <sub>3</sub> C-		II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	71.70 7.51 6.42 (71.67 7.91 6.60) (2)
100	(CH <sub>3</sub> ) <sub>3</sub> C-		II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	71.75 8.14 5.22 (72.23 8.08 5.11)

Example No.	R	R <sup>5</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
101	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> -C≡C-CH <sub>2</sub> -	H	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	72.84 8.55 2.83 (73.05 8.50 2.75)
102	(CH <sub>3</sub> ) <sub>3</sub> C-	Br(CH <sub>2</sub> ) <sub>4</sub> -	H	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	62.81 7.76 2.26 (62.83 7.82 2.36)
103	(CH <sub>3</sub> ) <sub>3</sub> C-	 -CH <sub>2</sub> -	H	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	72.74 8.30 2.49 (72.76 8.20 2.42)
104	(CH <sub>3</sub> ) <sub>3</sub> C-	 -	H	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	73.60 8.92 2.60 (73.71 8.81 2.61)
105	(CH <sub>3</sub> ) <sub>3</sub> C-	 -	H	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	70.10 8.94 2.56 (1) (70.36 8.77 2.56)
106	C <sub>2</sub> H <sub>5</sub> -	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> -	H	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	66.69 8.67 2.78 (5) (66.43 8.28 2.66)

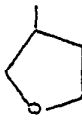


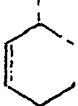


Example No.	R	R <sup>5</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
107	C <sub>2</sub> H <sub>5</sub> <sup>-</sup>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	H	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	71.20 9.00 3.14 (71.30 8.76 2.97)
108	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	4-C <sub>2</sub> H <sub>5</sub> (cis)	3-CO <sub>2</sub> CH <sub>3</sub> (cis)	71.60 8.95 2.73 (71.72 8.93 2.88)
109	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	5-CH <sub>3</sub> (cis)	3-CO <sub>2</sub> CH <sub>3</sub> (cis)	71.29 8.39 2.90 (71.30 8.76 2.97)
110	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	6-C <sub>2</sub> H <sub>5</sub> (cis)	3-CO <sub>2</sub> CH <sub>3</sub> (cis)	68.97 8.48 2.68 (6) (68.96 8.59 2.77)
111	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	6-CH <sub>3</sub> (cis)	3-CO <sub>2</sub> CH <sub>3</sub> (cis)	68.80 8.50 2.84 (68.96 8.48 2.87)
112	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	6-CH <sub>3</sub> (cis)	3-CO <sub>2</sub> CH <sub>3</sub> (cis)	71.39 8.88 2.74 (71.30 8.76 2.97)
113	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	6-CH <sub>3</sub> H	3-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	73.51 8.06 2.82 (1) (73.64 8.14 2.60)

Example No.	R	R <sup>5</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>14</sup>	Analysis % (Theoretical in brackets) C H N
114	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	II	4-CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub> (cis)	69.52 8.98 2.58 (69.87 8.80 2.72)
115	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> <sup>-</sup>	II	4-CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub> (cis)	72.49 8.88 2.70 (72.11 9.08 2.80)
116	CH <sub>3</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> -C≡C-CH <sub>2</sub> <sup>-</sup>	II	4-CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub> (cis)	69.19 8.78 3.42 (69.77 9.23 3.13)
117	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> -C≡C-CH <sub>2</sub> <sup>-</sup>	II	4-CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub> (cis)	72.84 8.55 2.63 (73.05 8.50 2.70)
118	CH <sub>3</sub> CH <sub>2</sub> <sup>-</sup>		II	4-CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub> (cis)	70.02 9.29 2.77 (1) (70.04 9.55 2.92)
119	(CH <sub>3</sub> ) <sub>3</sub> C <sup>-</sup>		II	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	71.06 8.40 2.88 (70.56 8.60 2.65)

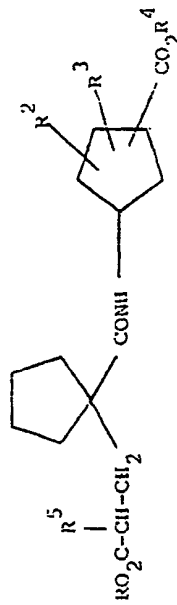
Example No.	R	R <sup>5</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
120	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O <sub>2</sub> C- 	H	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	70.22 8.08 2.11 (70.17 8.04 2.21) (7)
121	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O <sub>2</sub> C- 	H	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	75.40 8.18 2.07 (75.31 7.86 2.14)
122	(CH <sub>3</sub> ) <sub>3</sub> C-		H	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	66.79 9.52 3.08 (67.06 9.31 3.01)
123	(CH <sub>3</sub> ) <sub>3</sub> C-		H	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	62.98 8.67 2.97 (63.32 8.87 2.71) (1)
124	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> OCH <sub>2</sub> CH- 	H	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	67.01 9.84 2.98 (66.78 9.70 3.00)
125	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	H	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	73.57 8.49 2.58 (73.94 8.30 2.53) (1)

Example No.	R	R <sup>5</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
126	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O <sub>2</sub> CNHC-	H	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	66.52 8.18 5.10 (66.15 8.14 5.14)
127	(CH <sub>3</sub> ) <sub>3</sub> C-	$  \begin{array}{c}  \text{CH}_2\text{CH}_3 \\    \\  \text{C}_6\text{H}_5\text{CH}_2\text{NHC}-  \end{array}  $	H	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	69.46 9.22 5.14 (69.37 9.11 5.03)
128	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>2</sub> =CHCH <sub>2</sub> -	H	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	68.94 9.55 3.16 (68.93 9.49 3.22)
129	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> CH <sub>2</sub> CO-	H	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	66.47 9.27 2.84 (66.49 9.15 3.10)
130	(CH <sub>3</sub> ) <sub>3</sub> C-	(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> NHC-	H	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	73.38 8.87 4.42 (73.48 8.67 4.68)
131	C <sub>2</sub> H <sub>5</sub> -	CH <sub>2</sub> =CHCH <sub>2</sub> -	H	4-CO <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub> (cis)	68.92 9.33 3.16 (68.93 9.49 3.22)
132	(CH <sub>3</sub> ) <sub>3</sub> C-	(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub> NHC-	H	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	Ref. 0.5 (silica; Et <sub>2</sub> O, CH <sub>2</sub> Cl <sub>2</sub> 1:9)

Example No.	R	R <sup>5</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
133	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O <sub>2</sub> CNH-	H	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	66.06 8.20 4.92 (66.15 8.14 5.14)
134	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> C≡CCH <sub>2</sub> -	H	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	69.71 9.54 2.67 (69.45 9.64 3.12)
135	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	2-OH (cis)	4-CO <sub>2</sub> CH <sub>3</sub> (cis)	64.59 7.88 3.19 (64.91 7.88 2.79) (5)
136	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> -	H	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	64.34 9.37 3.35 (64.57 9.38 2.90)
137	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> -	H	3-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	67.55 8.71 2.73 (68.23 8.68 2.57)
138	(CH <sub>3</sub> ) <sub>3</sub> C-		H	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	65.73 9.12 2.75 (67.79 8.34 2.95) (2)
139	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> -C≡C-CH <sub>2</sub> -	H	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	67.43 8.99 3.33 (67.08 9.23 3.13)
140	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> -	H	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	71.08 8.67 2.88 (71.31 8.76 2.97)

Example No.	R	R <sup>3</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
141	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> -	II	3-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	70.57 7.81 2.25 (70.52 7.83 2.42)
142	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> -	II	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	66.73 8.35 2.59 (67.28 8.37 2.71)
143	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> -	II	3-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	73.42 8.13 2.71 (1) (73.64 8.14 2.60)
144	(CH <sub>3</sub> ) <sub>3</sub> C-		II	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	68.18 9.06 3.28 (68.71 8.89 3.34)
145	(CH <sub>3</sub> ) <sub>3</sub> C-		II	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	Rf. 0.73 (silica; ethyl acetate, toluene, 1:1)
146	(CH <sub>3</sub> ) <sub>3</sub> C-		II	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	Rf. 0.89 (silica; ethyl acetate)
147	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>4</sub> -	II	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	69.89 9.22 2.88 (2) (69.93 9.24 2.47)

Example No.	R	R <sup>5</sup>	R <sup>2</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
148	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>2</sub> =CH-CH <sub>2</sub> -	H	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	68.06 9.25 3.22 (1) (68.23 9.51 3.18)
149	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> -C≡C-CH <sub>2</sub> -	H	3-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> (cis)	71.56 8.34 2.64 (2) (7.78 8.55 2.70)
150	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> -	5-CH <sub>3</sub> (cis)	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	Rf. 0.92 (silica; ethyl acetate)
151	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> -	6-C <sub>2</sub> H <sub>5</sub> (cis)	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	7.14 8.92 2.77 (8) (70.73 8.92 2.74)



Example No.	R	R <sup>5</sup>	R <sup>2</sup>	R <sup>3</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
152	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	3-(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub> (cis)	H	3-CO <sub>2</sub> CH <sub>3</sub> (trans)	68.85 8.32 2.82 (68.81 8.66 2.77)
153	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> <sup>-</sup>	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	3-(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub> (cis)	5-OH (trans)	3-CO <sub>2</sub> CH <sub>3</sub> (trans)	66.36 8.38 2.63 (66.13 8.42 2.66)

(1) 0.25 hydrate

(2) 0.5 hydrate

(3) Solvate with 0.2 CH<sub>2</sub>Cl<sub>2</sub>

(4) Amine: T.P. Johnston et al, J. Med. Chem., 1971, 14 600

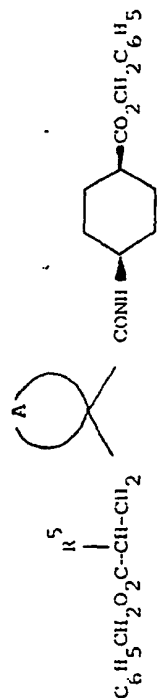
(5) Solvate with 0.1 CH<sub>2</sub>Cl<sub>2</sub>(6) Solvate with 0.5 CH<sub>2</sub>Cl<sub>2</sub>

(7) 0.75 hydrate

(8) Solvate with 0.143 CH<sub>2</sub>Cl<sub>2</sub>


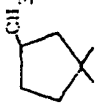
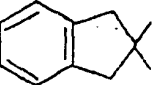


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Example No.	R <sup>5</sup>	(A)	Analysis % (Theoretical in brackets) C H N
154	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> -		73.82 7.50 2.61 (74.55 7.76 2.63)
155	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -		72.02 7.63 2.70 (72.37 7.55 2.56)
156	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -		72.01 7.95 2.35 (72.44 8.04 2.48)
157	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -		72.91 8.09 2.55 (72.70 7.72 2.49)

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Example No.	$R^5$		Analysis % (Theoretical in brackets) C H N
158	$CH_3O(CH_2)_2^-$		72.71 8.32 2.74 (72.44 8.05 2.48)
159	$CH_3O(CH_2)_2^-$		74.01 7.45 2.30 (74.34 7.25 2.34)

55 **EXAMPLE 160**

3{1-[(cis-4-Ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-ethylthiomethylpropanoic acid t-butyl ester

(a) Cyclopentane carboxylic acid dilithio dianion (prepared from cyclopentane carboxylic acid (2.58 g) as

described in Example 15) in tetrahydrofuran (100 ml) was treated with zinc chloride (1.85 g) at room temperature for 30 minutes, followed by t-butyl 2-bromomethylpropenoate (5.0 g) at -78° C. The reaction mixture was work d-up and the product purified as previously described to give 3-(1-carboxycyclopentyl)-2-methylenepropanoic acid t-butyl ester as an oil (5.1 g, 89%). Found: C,66.16; H,8.89. C<sub>14</sub>H<sub>22</sub>O<sub>4</sub> requires C,66.11; H,8.72%.

(b) Coupling of the above acid (4.96 g) with cis-4-aminocyclohexanecarboxylic acid ethyl ester (4.06 g) following the procedure of Example 81 gave 3-{1-[(cis-4-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-methylenepropanoic acid t-butyl ester as an oil (6.2 g, 78%). Found: C,67.94; H,9.35; N,3.54. C<sub>23</sub>H<sub>37</sub>NO<sub>5</sub> requires C,67.78; H,9.15; N,3.44%.

(c) The above diester (1.38 g, 3.4 mmole) was treated with neat ethanethiol (0.375 ml, 5.1 mmole) and N-benzyltrimethylammonium hydroxide, (7 drops). After 5 days under nitrogen the mixture was dissolved in diethyl ether, washed with dilute hydrochloric acid, dilute sodium bicarbonate, and water, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated to give a yellow oil (1.09 g). Chromatography on silica eluting with a mixture of diethyl ether and dichloromethane gave the title product as an oil (0.51 g, 32%). Found: C,64.23; H,9.14; N,2.98. C<sub>25</sub>H<sub>43</sub>NO<sub>5</sub>S requires C,63.93; H,9.23; N,2.98%.

#### EXAMPLE 161

3-{1-[(cis-4-Ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-ethylsulphonylmethylpropanoic acid t-butyl ester

meta-Chloroperbenzoic acid (0.36 g, 2.09 mmole) was added to a stirred solution of 3-{1-[(cis-4-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-ethylthiomethylpropanoic acid t-butyl ester (0.49 g, 1.04 mmole) in dichloromethane (25 ml) at 0° C. The solution was stirred at room temperature for 16 hours, further meta-chloroperbenzoic acid (0.36 g) added and the solution stirred for a further 24 hours. The reaction mixture was diluted with dichloromethane (25 ml), washed with dilute sodium bicarbonate, water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated. The residue was chromatographed on silica eluting with a mixture of diethyl ether and dichloromethane to give the title sulphone as a white crystalline solid (0.38 g, 73%). Found: C,59.49; H,8.73; N,2.64. C<sub>25</sub>H<sub>43</sub>NO<sub>7</sub>S requires C,59.85; H,8.64; N,2.79%.

#### EXAMPLE 162

3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-carboxyethyl)propanoic acid benzyl ester

3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-[2-(t-butoxycarbonyl)ethyl]propanoic acid benzyl ester (3.72 g, 6 mmole) was dissolved in trifluoroacetic acid (35 ml) and stored at 0° C for 24 hours. The reaction mixture was poured into iced water and extracted with dichloromethane. The organic phase was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under vacuum. The residue was crystallised from a mixture of diethyl ether and hexane to give a white solid (1.93 g) which was recrystallised from diethyl ether to give the title acid as a white solid (1.43 g, 42%), m.p. 103-104° C. Found: C,70.16; H,7.47; N,2.45. C<sub>33</sub>H<sub>41</sub>NO<sub>7</sub> requires C,70.31; H,7.33; N,2.49%.

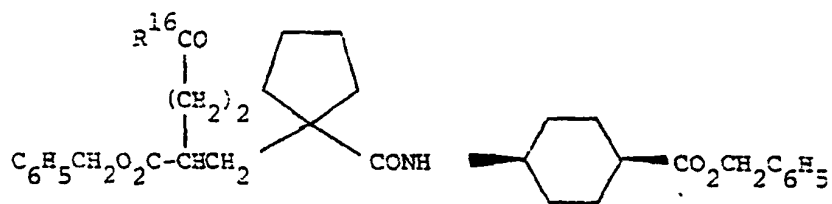
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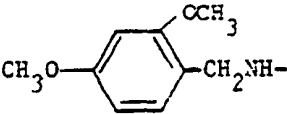
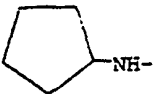
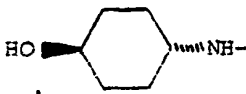
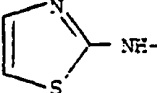
3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-isopropylcarbamylethyl)propanoic acid benzyl ester

3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-carboxyethyl)propanoic acid benzyl ester (0.41 g, 0.73 mmole) was dissolved in dry dichloromethane (20 ml) and treated sequentially at room temperature with 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (0.28 g, 1.46 mmole), N-methylmorpholine (0.22 g, 2.18 mmole), and 1-hydroxybenzotriazole (0.10 g, 0.74 mmole). After stirring for 10 minutes, isopropylamine (0.065 g, 94 mmole) was added and the mixture stirred for 18 hours at room temperature under nitrogen. The reaction mixture was diluted with dichloromethane and the organic phase washed in turn with water, dilute hydrochloric acid and aqueous sodium hydrogen carbonate, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under vacuum to give an oil (0.46 g). Column chromatography on silica gel eluting with dichloromethane and diethyl ether-dichloromethane mixtures yielded the title propanoic acid derivative as an oil (0.09 g, 20%). R<sub>f</sub> 0.65 (silica; methanol, dichloromethane 1:9).

#### EXAMPLES 164-169

The following compounds were prepared following the procedure of Example 163 using the appropriate amine. The products were isolated as gums.



Example No.	$R^{16}$	Analysis % (Theoretical in brackets) C            H            N		
164		Rf 0.6 (silica; Et <sub>2</sub> O)		
165	$(CH_3)_2N-$	Rf 0.6 (silica; Et <sub>2</sub> O)		
166	$CH_3NH-$	70.65      7.66      4.83 (70.81      7.69      4.86)		
167		72.17      8.10      4.61 (72.35      7.99      4.44)		
168		70.25      7.89      4.19 (70.88      7.93      4.24)		
169		66.67      6.86      6.31 (66.95      6.71      6.51)		

## 55 EXAMPLE 170

3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-carbamylethyl)propanoic acid benzyl ester

3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-{2-[(2,4-dimethoxyphenyl)-methylcarbamoyl]ethyl}-propanoic acid benzyl ester (Example 164) (0.37 g, 0.52 mmole) was dissolved in trifluoroacetic acid (10 ml). After stirring for 18 hours at room temperature the deep pink reaction mixture was poured into iced water which was basified with sodium hydrogen carbonate and extracted with dichloromethane. The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under vacuum. The residue was purified by column chromatography on silica gel eluting with dichloromethane-diethyl ether and methanoldichloromethane mixtures to yield the title ester (110 mg, 38%). Rf 0.25 (silica; ethylacetate).

#### EXAMPLE 171

3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-(butanoylamino)propanoic acid benzyl ester

A solution of 3-{1-[(cis-4-benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(t-butoxycarbonylamino)propanoic acid benzyl ester (0.71 g, 1.2 mmole) in diethyl ether (50 ml) at 0 °C was saturated with gaseous hydrogen chloride. After 2 hours at room temperature the solvent was evaporated under vacuum and the resulting residue dissolved in dry dichloromethane (30 ml). Triethylamine (0.16 ml, 5.9 mmole) was added at 0 °C followed by butanoyl chloride (0.18 ml, 1.8 mmole). After stirring for 16 hours at room temperature additional butanoyl chloride (0.18 ml, 1.8 mmole) was added and stirring was continued for 0.75 hours. The reaction mixture was washed in turn with dilute aqueous sodium bicarbonate, 1N sodium hydroxide solution and water, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated under vacuum. The crude product was purified by column chromatography on silica gel eluting with diethyl ether-dichloromethane mixtures, followed by preparative layer chromatography (development with 10% methanol-dichloromethane) to give the title amide (0.15 g, 22%). Rf 0.7 (silica; methanol, dichloromethane 1:9).

#### EXAMPLE 172

3-{1-[(cis-4-Ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(2-methylsulphonyl)ethyl)propanoic acid benzyl ester

meta-Chloro-perbenzoic acid (0.17 g, 80%) was added to a solution of 2-(2-methylthioethyl)-3-{1-[(cis-4-benzoyloxycarbonylcyclohexyl)carbamoyl]cyclopentyl}propanoic acid benzyl ester (0.2 g) in dichloromethane (5 ml) at room temperature, and the reaction mixture stirred for 3 days. The mixture was evaporated to dryness under reduced pressure and the residue partitioned between ether and aqueous sodium hydrogen carbonate (5%). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to yield the crude product as an oil (0.2 g). Chromatography over silica gel, eluting with a mixture of hexane and ethyl acetate (1:3) gave the sulphone as an oil (0.15 g). Found: C,60.20; H,7.60; N,2.48. C<sub>29</sub>H<sub>41</sub>NO<sub>6</sub>S requires C,60.74; H,7.83; N,2.53%.

#### EXAMPLE 173

2-(Carboxymethyl)-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester

2-(Benzoyloxycarbonylmethyl)-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester (3.50 g, 6.45 mmole) was dissolved in tetrahydrofuran (100 ml) and stirred with 5% palladium on carbon catalyst (200 mg) at room temperature under hydrogen at 50 p.s.i. (3.5 bar). After 36 hours the catalyst was removed by filtration and the solvent evaporated to give the product as a colourless oil (2.8 g, 96%). Found: C,63.28; H,8.70; N,3.20. C<sub>24</sub>H<sub>39</sub>NO<sub>7</sub> requires C,63.55; H,8.67; N,3.09%.

#### EXAMPLE 174

3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(morpholinocarbonylmethyl)propanoic acid t-butyl ester

2-(Carboxymethyl)-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester (1.0 g, 2.21 mmole) was added to a solution of morpholine (230 mg, 2.65 mmole), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride salt (845 mg, 4.41 mmole), 1-hydroxybenzotriazole hydrate (675 mg, 4.41 mmole) and triethylamine (893 mg, 8.84 mmole) in dry dichloromethane (50 ml) at room temperature. After 4 days the solvent was evaporated and the residue taken up in ethyl acetate (50 ml) and washed with 1N hydrochloric acid (50 ml), water (50 ml) and saturated sodium hydrogen carbonate solution (50 ml). The organic layer was separated, dried over magnesium sulphate and evaporated to give

an orange oil. Chromatography on silica gel eluting with diethyl ether followed by ethyl acetate gave the title product as a yellow foam (790 mg, 68%). Found: C,64.63; H,9.09; N,5.23.  $C_{28}H_{46}N_2O_7$  requires C,64.34; H,8.87; N,5.36%.

#### 5 EXAMPLE 175

3-{1-[(cis-4-Ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-[(2-methoxyethyl)carbamoylmethyl]-  
propanoic acid t-butyl ester

The procedure of Example 174 was followed using 2-methoxyethylamine instead of morpholine to give  
10 the title product as a pale yellow oil (740 mg, 66%). Found: C,63.77; H,9.32; N,5.28.  $C_{27}H_{46}N_2O_7$  requires C,63.50; H,9.08; N,5.49%.

#### EXAMPLE 176

2-(2-Acetonyl)-3-{1-[(cis-4-benzyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester

15 3-{1-[(cis-4-benzyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-propenyl)propanoic acid t-butyl ester (400 mg, 0.80 mmole) was dissolved in a mixture of water (0.7 ml) and dimethylformamide (5 ml) and was stirred with palladium dichloride (15 mg) and cupric chloride (25 mg) at 60 °C for 18 hours whilst bubbling air through the solution. The solution was cooled, diethyl ether (20 ml) and 1N hydrochloric acid  
20 (20 ml) were added and the layers separated. The aqueous layer was extracted with more diethyl ether (20 ml) and the organic layers were combined, dried over magnesium sulphate, evaporated and the residue chromatographed on silica gel eluting with a mixture of diethyl ether and pentane (2:1 by volume). The appropriate fractions were combined and evaporated to give the title product as a pale yellow oil (210 mg, 51%). Rf 0.2 (silica; diethyl ether, hexane 2:1).

#### 25 EXAMPLE 177

2-(2-Acetonyl)-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester

3-{1-[(cis-4-Ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-propenyl)propanoic acid t-butyl es-  
30 ter was oxidised following the procedure described in Example 176 to give the title product. Found: C,66.00; H,9.16; N,3.15.  $C_{25}H_{41}NO_6$  requires C,66.49; H,9.15; N,3.10%.

#### EXAMPLE 178

2-(2-N-Benzylaminopropyl)-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-  
35 butyl ester. Diastereomers A and B

2-(2-Acetonyl)-3-{1-[(cis-4-ethoxycarbonyl)cyclohexyl]carbamoyl]cyclopentyl}propanoic acid t-butyl ester (1.00 g, 2.2 mmole) was dissolved in methanol (20 ml) and treated sequentially with benzylamine (1.5 ml, 13.8 mmole), 5N methanolic hydrogen chloride (0.8 ml) and sodium cyanoborohydride (0.14 g, 2.2 mmole)  
40 and 3A molecular sieves (10 ) were added. The black solution was stirred for 16 hours at room temperature. Further sodium cyanoborohydride (0.23 g, 3.7 mmole) was added and the pH of the solution adjusted to 7 with 5N methanolic hydrogen chloride and benzylamine. After 16 hours the solvent was removed under vacuum and the residue partitioned between ethyl acetate and 1M aqueous sodium carbonate. The aqueous phase was extracted with ethyl acetate (4 x 50 ml) with the use of sodium chloride to disperse emulsions.  
45 The organic phases were dried ( $MgSO_4$ ) and evaporated to give an orange oil (4 g). Purification by column chromatography on silica, eluting with ethyl acetate-hexane mixtures yielded the two title diastereomers. Diastereomer A (490 mg, 41%) Rf. 0.41 (silica; methanol, ethyl acetate, 5:95). Found: C,70.52; H,9.52; N,5.62.  $C_{32}H_{50}N_2O_5$  requires C,70.81; H,9.29; N,5.16%. Diastereomer B (650 mg, 54%) Rf. 0.27 (silica; methanol, ethyl acetate, 5:95). Found: C,70.75; H,9.22; N,5.49.  $C_{32}H_{50}N_2O_5$  requires C,70.81; H,9.92;  
50 N,5.16%.

#### EXAMPLE 179

2-(1-N-Benzylaminopropyl)-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-  
butyl ester

55 The title compound was prepared from 2-propionyl-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester by the procedure of Example 178 to give an oil. Found: C,70.96; H,9.47; N,5.22.  $C_{32}H_{50}N_2O_5$  requires C,70.81; H,9.29; N,5.16%.

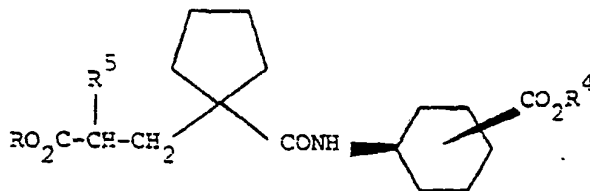
EXAMPLE 180

2-Ethylaminomethyl-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester

- 5 2-(N-Benzyl-N-ethylaminomethyl)-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-propanoic acid t-butyl ester (3.38 g, 6.2 mmole) was dissolved in ethanol (70 ml) and hydrogenated at 30 p.s.i. (2 bar) over 20% palladium hydroxide on carbon at room temperature for 16 hours. The catalyst was removed by filtration through an Arbacell pad and the filtrate evaporated under vacuum. The residue was chromatographed on silica eluting with methanol-dichloromethane mixtures to give the title compound as an  
 10 oil (2.35 g, 83%). Found: C,65.51; H,9.57; N,6.14.  $C_{25}H_{44}N_2O_5 \cdot 0.1 CH_2Cl_2$  requires C,65.37; H,9.66; N,6.08%.

EXAMPLES 181-185

- 15 The following Examples were prepared by the general procedure of Example 180 starting with the appropriate N-benzylamine for Examples 181-183 and the appropriate N,N-dibenzylamine for Examples 184, and 185.





Example No.	R	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
181	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_3 \\   \\ \text{NH}_2\text{-CH-CH}_2\text{-} \\   \\ \text{Diastereomer A} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	Rf. 0.23 (silica; CH <sub>2</sub> Cl <sub>2</sub> , CH <sub>3</sub> OH, NH <sub>4</sub> OH, 90:10:1)
182	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_3 \\   \\ \text{NH}_2\text{-CH-CH}_2\text{-} \\   \\ \text{Diastereomer B} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	Rf. 0.20 (silica; CH <sub>2</sub> Cl <sub>2</sub> , CH <sub>3</sub> OH, NH <sub>4</sub> OH, 90:10:1)
183	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_2\text{CH}_3 \\   \\ \text{NH}_2\text{-CH-} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	Rf. 0.41 + 0.39 (silica; CH <sub>2</sub> Cl <sub>2</sub> , CH <sub>3</sub> OH, NH <sub>4</sub> OH, 90:10:1)

Example No.	R	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
184	(CH <sub>3</sub> ) <sub>3</sub> C-	NH <sub>2</sub> CH <sub>2</sub> -	4-CO <sub>2</sub> C <sub>11</sub> H <sub>5</sub> (cis)	64.80 9.28 6.76 (65.08 9.50 6.60)
185	(CH <sub>3</sub> ) <sub>3</sub> C-	NH <sub>2</sub> CH <sub>2</sub> -	3-CO <sub>2</sub> C <sub>11</sub> H <sub>5</sub> (cis)	64.76 9.63 6.55 (65.06 9.50 6.60)

## 55 EXAMPLE 186

2-Amino-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester

2-Benzyloxycarbonylamino-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-propanoic

acid t-butyl ester (8.11 g, 15 mmole) in 10% aqueous ethanol (320 ml) was hydrogenated at 30 p.s.i. (2 bar) for 4 hours over 10% palladium on carbon. The catalyst was removed by filtration and the filtrate evaporated under vacuum. The residue was azeotroped with dichloromethane (3 x 50 ml) and dried to give the crude title compound as a gum (6.86 g). Rf. 0.6 (silica; methanol, dichloromethane 5:95).

5

**EXAMPLE 187**

2-Amino-3-{1-[(cis-3-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester

Hydrogenation of 2-benzyloxycarbonylamino-3-{1-[(cis-3-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester as described above gave the title amine as a gum. Found: C,64.75; H,9.35; N,6.36.  $C_{22}H_{38}N_2O_5$  requires C,64.36; H,9.33; N,6.82%.

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**EXAMPLE 183**

2-Benzenesulphonamido-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester

15

2-Amino-3-{1-[(cis-4-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester (0.605 g, 1.48 mmole) was dissolved in dry dichloromethane (25 ml) and treated at 0 °C with triethylamine (0.45 g, 4.4 mmole) and benzene sulphonyl chloride (0.24 ml, 1.84 mmole). After stirring for 16 hours at room temperature under nitrogen the dichloromethane was removed under vacuum, the residue taken up in diethyl ether (25 ml), washed with dilute hydrochloric acid, dilute sodium hydrogen carbonate and water, dried ( $Na_2SO_4$ ) and the solvent evaporated under vacuum to give the crude product. Purification by column chromatography on silica, eluting with diethyl ether-dichloromethane mixtures, gave pure title compound as a white foam (0.60 g, 74%). Found: C,61.38; H,7.85; N,5.06.  $C_{28}H_{42}N_2O_7S$  requires C,61.06; H,7.69; N,5.09%.

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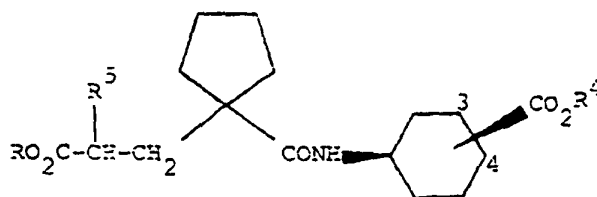
**EXAMPLE 189-213**

The following compounds were prepared following the general procedure of Example 188 starting with the appropriate amine and reacting with the appropriate sulphonyl chloride to yield the sulphonamide products or with an acid chloride, isocyanate, chloroformate or N-(aryloxycarbonyloxy)-succinimide to yield the amide, urea, alkoxycarbonylamino or aralkyloxycarbonylamino products respectively. The products are cis-3- and cis-4-cyclohexane carboxylic acid esters.

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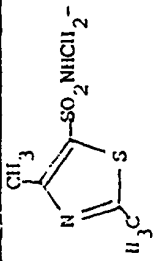
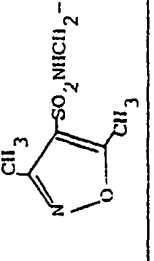
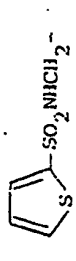
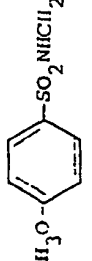
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Example No.	R	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Form Isolated	Analysis % (Theoretical in brackets) C H N
189	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CONH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Solid m.p. 122-126°C	68.15 8.36 5.17 (68.15 8.39 5.30)
190	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NHCONH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	65.87 8.37 7.58 (66.27 8.34 7.73)
191	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub> NH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	57.65 8.60 5.30 (58.11 8.58 5.42)
192	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SO <sub>2</sub> NH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	white solid m.p. 133-135°C	61.59 7.94 4.69 (61.67 7.85 4.96)
193	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_2\text{CH}_3 \\   \\ \text{C}_6\text{H}_5\text{CH}_2\text{OCONCH}_2- \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	67.51 8.55 5.02 (67.55 8.59 4.78)
194	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_2\text{CH}_3 \\   \\ \text{CONCH}_2- \\   \\ \text{C}_5\text{H}_4\text{O} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	65.74 8.52 5.21 (65.91 8.48 5.13)

Example No.	R	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Form Isolated	Analysis % (Theoretical in brackets) C H N
195	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_2\text{CH}_3 \\   \\ \text{CH}_3\text{SO}_2\text{NCH}_2- \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil (0.5 H <sub>2</sub> O)	57.67 8.48 5.17 (57.45 8.54 5.12)
196	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_3 \\   \\ \text{C}_6\text{H}_5\text{CH}_2\text{OCONH-CHCH}_2- \\ \text{Diastereomer A} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	solid m.p. 89-90°C	67.87 9.09 4.67 (67.55 8.59 4.58)
197	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_3 \\   \\ \text{C}_6\text{H}_5\text{CH}_2\text{OCONH-CHCH}_2- \\ \text{Diastereomer B} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil (0.25 CH <sub>2</sub> Cl <sub>2</sub> )	65.71 8.51 4.60 (65.68 8.37 4.61)
198	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3\text{OCONH-CHCH}_2- \\ \text{Diastereomer A} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	solid m.p. 122-124°C	62.96 8.77 5.06 (63.50 9.08 5.49)
199	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3\text{OCONH-CHCH}_2- \\ \text{Diastereomer B} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	63.04 8.66 4.83 (63.50 9.08 5.49)

Example No.	R	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Form Isolated	Analysis % (Theoretical in brackets) C H N
200	(CH <sub>3</sub> ) <sub>3</sub> C-	$\begin{array}{c} \text{CH}_2\text{CH}_3 \\   \\ \text{C}_6\text{H}_5\text{CH}_2\text{CONH}-\text{CH}- \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil (0.08 CH <sub>2</sub> Cl <sub>2</sub> )	66.90 8.34 4.61 (66.91 8.52 4.72)
201	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CONHCH <sub>2</sub> -	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	67.87 8.40 5.29 (68.15 8.39 5.30)
202	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> CONHCH <sub>2</sub> -	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil (0.3 H <sub>2</sub> O)	63.56 9.03 6.15 (63.53 9.10 5.93)
203	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub> NHCH <sub>2</sub> -	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	58.54 8.48 5.50 (58.84 8.74 5.28)
204	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub> NHCH <sub>2</sub> -	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	60.55 7.89 4.87 (61.68 7.85 4.96)
205	(CH <sub>3</sub> ) <sub>3</sub> C-	CF <sub>3</sub> SO <sub>2</sub> NH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	solid m.p. 111-113°C.	50.88 7.20 4.97 (50.91 6.87 5.16)
206	(CH <sub>3</sub> ) <sub>3</sub> C-	CF <sub>3</sub> SO <sub>2</sub> NHCH <sub>2</sub> -	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	52.33 7.28 5.00 (51.79 7.06 5.03)

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Example No.	R	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Form Isolated	Analysis: % (Theoretical in brackets) C H N
207	(CH <sub>3</sub> ) <sub>3</sub> C-	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub> NH-	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	58.30 8.81 5.57 (58.11 8.58 5.42)
208	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub> NHCH <sub>2</sub> -	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam (0.5 H <sub>2</sub> O)	60.62 7.98 4.96 (60.71 7.91 4.88)
209	(CH <sub>3</sub> ) <sub>3</sub> C-		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil (0.25 H <sub>2</sub> O)	55.54 7.45 6.65 (55.65 7.59 6.95)
210	(CH <sub>3</sub> ) <sub>3</sub> C-		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil (0.25 H <sub>2</sub> O)	57.14 7.72 7.05 (57.17 7.80 7.14)
211	(CH <sub>3</sub> ) <sub>3</sub> C-	C <sub>6</sub> H <sub>5</sub> CONHCH <sub>2</sub> -	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	67.52 8.35 5.27 (67.57 8.41 5.25)
212	(CH <sub>3</sub> ) <sub>3</sub> C-		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	56.39 7.51 4.75 (56.82 7.42 4.91)
213	(CH <sub>3</sub> ) <sub>3</sub> C-		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	60.77 7.72 4.78 (60.58 7.80 4.71)

55 **EXAMPLE 214**  
 3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(4-hydroxybutyl)propanoic acid t-butyl ester

2-(4-Benzyloxybutyl)-3-(1-carboxycyclopentyl)propanoic acid t-butyl ester (1 g, 2.48 mmole) was dissolved in ethanol (35 ml) and stirred at room temperature with 5% palladium on carbon catalyst (250 mg) under hydrogen at 50 p.s.i. (3.45 bar). After 3 hours the catalyst was removed by filtration and the solvent evaporated. The residue was dissolved in dichloromethane (40 ml) and cis-4-amino-cyclohexanecarboxylic acid benzyl ester p-toluene sulphonate salt (1.5 g, 3.70 mmole), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride salt (1.22 g, 6.37 mmole), 1-hydroxybenzotriazole hydrate (0.97 g, 6.34 mmole) and triethylamine (1.28 g, 12.65 mmole) added. After 3 days at room temperature, the solvent was evaporated and the residue dissolved in ethyl acetate (50 ml). The solution was washed with water (50 ml), 1N hydrochloric acid (50 ml), water (50 ml) and saturated sodium hydrogen carbonate solution (50 ml), dried over magnesium sulphate and the solvent evaporated. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and pentane (1:1 by volume) and the appropriate fractions combined and evaporated to give the title product as a pale orange oil (912 mg, 61%). Found: C,70.29; H,8.94; N,2.64.  $C_{31}H_{47}NO_6$  requires C,70.05; H,9.08; N,2.59%.

#### 15 EXAMPLE 215

3-{1-[(cis-4-Benzyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(4-pentanoyloxybutyl)propanoic acid t-butyl ester

Valeryl chloride (0.2 ml, 1.98 mmole) was added dropwise to a stirred, ice cold solution of 3-{1-[(cis-4-benzyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(4-hydroxybutyl)propanoic acid t-butyl ester (0.7 g, 1.32 mmole) in dry pyridine (5 ml). The mixture was allowed to stand overnight at room temperature and ice was added, the pH was adjusted to 3 by the addition of 2N hydrochloric acid and the mixture was extracted with diethyl ether. The organic extract was dried ( $Na_2SO_4$ ) and evaporated to give a gum which was chromatographed on silica eluting with hexane containing increasing proportions of diethyl ether to give the title product as a gum. Found: C,70.06; H,8.91; N,2.58.  $C_{36}H_{55}NO_7$  requires C,70.44; H,9.03; N,2.28%.

#### EXAMPLE 216

2-(4-Azidobutyl)-3-{1-[(cis-4-benzyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester

2-(4-Bromobutyl)-3-1-[(cis-4-benzyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl propanoic acid t-butyl ester (3.1 g, 5.24 mmole) was added to a solution of tetramethylguanadinium azide (1.4 g, 8.86 mmole) and potassium iodide (60 mg) in chloroform (60 ml). The solution was heated under reflux for 3 days, and was then washed with water (2 x 50 ml), dried over magnesium sulphate and the solvent evaporated to give the product as a yellow oil (2.9 g, 100%). Found: C,66.86; H,8.40; N,9.85.  $C_{31}H_{46}N_4O_5$  requires C,67.12; H,8.36; N,10.10%.

#### EXAMPLE 217

3-{1-[(cis-4-Carboxy-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethyl)propanoic acid

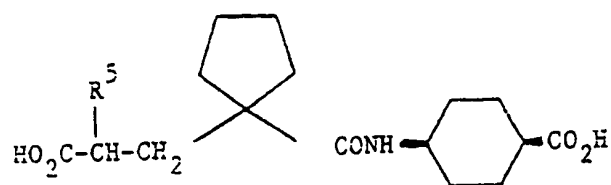
3-{1-[(cis-4-Benzyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethyl)propanoic acid benzyl ester (1.08 g) in absolute ethanol (30 ml) and water (20 ml) was hydrogenated at room temperature over 5% palladium on charcoal catalyst (200 mg) at 30 p.s.i. pressure for two hours. The reaction mixture was filtered through a short column of Avicel and the solvent evaporated under reduced pressure. The residue was taken up in 1N sodium hydroxide (4 ml) and washed with ether. The aqueous layer was acidified with 2N hydrochloric acid and extracted with methylene chloride. The organic extracts were washed with water, dried ( $MgSO_4$ ) and evaporated under reduced pressure to give the required diacid as a white foam (620 mg, 83%). Found: C,60.07; H,7.64; N,4.07.  $C_{19}H_{31}NO_6 \cdot 0.05 CH_2Cl_2 \cdot 0.5H_2O$  requires C,59.89; H,8.46; N,3.67%.

#### 50 EXAMPLES 218 - 234

The following compounds were prepared by the procedure of Example 217 starting with the appropriate dibenzyl ester.



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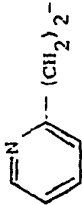
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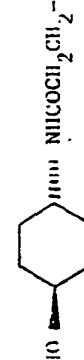
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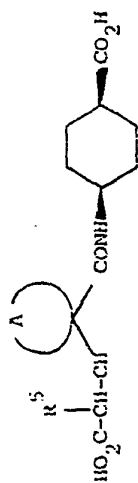
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Example No.	R <sup>S</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
218	$\text{CH}_3(\text{CH}_2)_2^-$	Foam	64.26 8.92 3.84 (64.56 8.84 3.96)
219	$\text{C}_6\text{H}_5(\text{CH}_2)_2^-$	Foam (0.1 $\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$ , 0.7 $\text{CH}_2\text{Cl}_2$ )	68.23 8.02 3.16 (68.33 7.95 3.26)
220		Foam (1.16 $\text{H}_2\text{O}$ )	63.64 7.83 5.80 (63.18 7.85 6.40)
221	$(\text{CH}_3)_3\text{CO}_2\text{C}(\text{CH}_2)_2^-$	Foam (0.75 $\text{H}_2\text{O}$ )	60.82 8.66 3.16 (60.97 8.57 3.09)
222	$(\text{CH}_3)_2\text{CHNICO}(\text{CH}_2)_2^-$	Foam (0.75 $\text{H}_2\text{O}$ )	60.38 8.55 5.84 (60.32 8.63 6.40)
223	$(\text{CH}_3)_2\text{NCO}(\text{CH}_2)_2^-$	Foam (1.25 $\text{H}_2\text{O}$ )	58.27 8.65 5.90 (58.25 8.50 6.47)
224	$\text{CH}_3\text{NICO}(\text{CH}_2)_2^-$	Foam (0.75 $\text{H}_2\text{O}$ )	58.85 8.17 6.29 (58.59 8.23 6.83)

Example No.	R <sup>5</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
225	$\text{H}_2\text{NCO}(\text{CH}_2)_2^-$	Foam (1.5 H <sub>2</sub> O)	56.26 8.08 6.19 (55.73 8.12 6.84)
226	$\text{C}_6\text{H}_5\text{CONH}-$	Solid m.p. 208-9°C	64.25 7.49 6.00 (64.17 7.02 6.51)
227	$\text{CF}_3\text{CONH}-$	Solid m.p. 136°C (dec.) (0.75 H <sub>2</sub> O)	49.68 6.41 6.13 (49.60 6.13 6.43)
228	$\text{CH}_3(\text{CH}_2)_2\text{CONH}-$	Solid (0.25 H <sub>2</sub> O)	59.77 8.17 6.77 (59.90 8.17 6.99)
229		Foam (0.5 H <sub>2</sub> O)	62.98 8.63 5.77 (62.72 8.55 6.10)
230		Foam (0.25 H <sub>2</sub> O)	61.65 8.24 5.33 (61.90 8.42 5.77)
231	$\text{HO}_2\text{C}(\text{CH}_2)_2^-$	Foam (0.25 H <sub>2</sub> O)	58.91 8.06 3.32 (58.83 7.67 3.61)

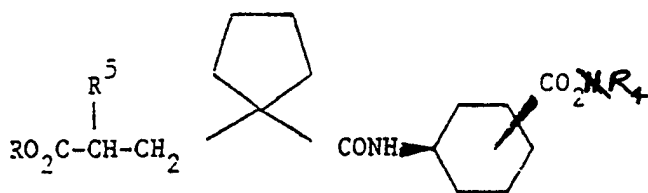
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Example No.	R <sup>5</sup>	(A)	Isolated Form	Analysis % (Theoretical in brackets) C H N
232	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -		gum	61.75 8.53 3.55 (62.64 8.67 3.65)
233	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -		foam	62.60 8.94 3.10 (62.64 8.67 3.65)
234	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -		foam (collapses at 70°C)	65.94 8.04 3.30 (66.16 7.49 3.36)

55 EXAMPLES 235 - 240

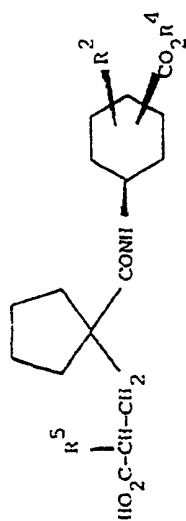
The following compounds were prepared by the procedure of Example 217 starting with the appropriate mono or dibenzyl ester



Example No.	R	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
235	H	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	3-CO <sub>2</sub> H	64.45 8.83 3.93 (64.56 8.84 3.96)
236	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> <sup>-</sup>	4-CO <sub>2</sub> H	61.80 8.64 3.28 (61.81 8.72 3.28)
237	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	4-CO <sub>2</sub> H	65.22 9.35 3.73 (1) (65.09 9.28 3.61)
238	H	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> <sup>-</sup>	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	65.88 9.36 3.46 (66.11 9.25 3.69)

(1) 0.3 H<sub>2</sub>O

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Example No.	R <sup>5</sup>	R <sup>2</sup>	CO <sub>2</sub> R <sup>4</sup>	Analysis % (Theoretical in brackets) C H N
239	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> -	5-CH <sub>3</sub> (cis)	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	RF 0.8 (silica; ethyl acetate)
240	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> -	6-C <sub>2</sub> H <sub>5</sub> (cis)	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (cis)	RF 0.67 (silica; ethyl acetate)

55 **EXAMPLE 241**  
3-{1-[(cis-4-Ethoxycarbonyl)cyclohexyl]carbamoyl}cyclopentyl}-2-[3-(N-methylcarbamoyl)phenylmethyl]-  
propanoic acid tert-butyl ester

3-{1-[(cis-4-Ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-[3-(benzyloxycarbonyl)phenylmethyl]-propanoic acid tert-butyl ester (370 mg, 0.60 mmole) was dissolved in tetrahydrofuran (30 ml) and was stirred with 5% palladium on carbon catalyst (50 mg) under an atmosphere of hydrogen at 50 p.s.i. (3.45 bar) for 5 hours. Further catalyst (50 mg) was added and the hydrogenation was continued for 48 hours.

5 The catalyst was removed by filtration and the solvent evaporated to give a yellow oil. Chromatography on silica gel eluting with a mixture of methanol and ethyl acetate (1:4 to 1:1 by volume) gave a colourless oil. The oil (240 mg) was added to a solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (170 mg, 0.91 mmole), 1-hydroxybenzotriazole (140 mg, 0.91 mmole), triethylamine (182 mg, 1.80 mmole) and methylamine hydrochloride (31 mg, 0.45 mmole) in dry methylene chloride (20 ml), and the mixture

10 was stirred at room temperature for 6 days. The solvent was evaporated under reduced pressure and the residue partitioned between ethyl acetate and water. The aqueous layer was acidified with 2N hydrochloric acid, separated and extracted three times with ethyl acetate. The organic fractions were combined and washed sequentially with saturated aqueous sodium bicarbonate solution, water and brine. Drying ( $\text{MgSO}_4$ ) and evaporation under reduced pressure gave a yellow oil which was chromatographed on silica gel eluting

15 with a mixture of ethyl acetate and pentane (1:1 by volume). Azeotroping with methylene chloride gave the desired amide as a colourless oil (200 mg, 80%). Found: C,67.58; H,8.80; N,5.22.  $\text{C}_{31}\text{H}_{46}\text{N}_2\text{O}_6 \cdot 1/8 \text{CH}_2\text{Cl}_2$  requires: C,67.57; H,8.42; N,5.06%.

## EXAMPLE 242

20 3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(methoxymethyl)propanoic acid

3-{1-[(cis-4-benzyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(methoxymethyl)propanoic acid t-butyl ester (483 mg, 0.96 mmole) was dissolved in dry trifluoroacetic acid (5 ml) at 0°C. After 18 hours, the solvent was evaporated and the resulting oil azeotroped with dichloromethane (4 x 20 ml). The oil was taken

25 up in dichloromethane (50 ml) and washed with water (7 x 50 ml) until the washings were neutral. The organic solution was dried over magnesium sulphate and the solvent evaporated to give a colourless oil (415 mg, 97%). Found: C,65.07; H,7.66; N,3.05.  $\text{C}_{25}\text{H}_{35}\text{NO}_6 \cdot 0.75 \text{H}_2\text{O}$  requires C,65.41; H,8.01; N,3.05%.

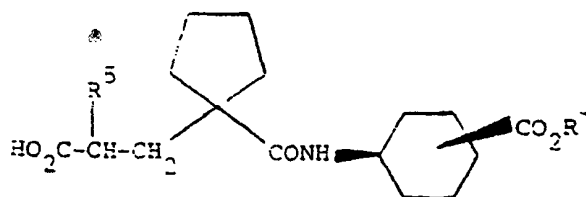
## EXAMPLES 243 - 314

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The following compounds were prepared by the procedure of Example 242 starting with the appropriate ester of formula (V) wherein  $\text{R}^{13}$  is t-butyl. The compounds are cis-3- and cis-4-cyclohexane-carboxylic acid esters.

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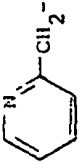
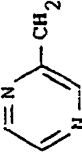


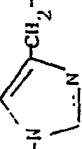
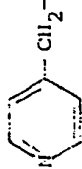
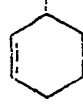
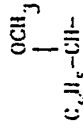
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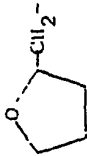
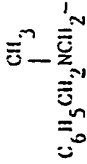
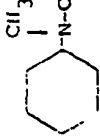
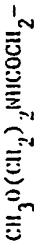
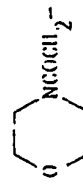
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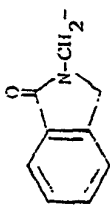
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Example No.	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
243	CH <sub>3</sub> CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	oil	68.72 8.23 2.86 (68.47 8.30 2.96)
244	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>3</sub> -	4-CO <sub>2</sub> -CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	oil (0.75 H <sub>2</sub> O)	66.61 8.22 2.88 (66.57 8.38 2.88)
245	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> -	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	oil (0.25 H <sub>2</sub> O)	65.69 8.10 2.79 (65.63 8.06 2.83)
246		4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	gum	Rf 0.7 (silica; CH <sub>2</sub> Cl <sub>2</sub> , CH <sub>3</sub> OH, CH <sub>3</sub> CO <sub>2</sub> H 90:10:1)
247		4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	gum	Rf 0.7 (silica; CH <sub>2</sub> Cl <sub>2</sub> , CH <sub>3</sub> OH, CH <sub>3</sub> CO <sub>2</sub> H 90:10:1)
248	CH <sub>2</sub> =CH-CH <sub>2</sub> -	4-CO <sub>2</sub> -CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	oil	Rf 0.7 (silica; CH <sub>3</sub> CO <sub>2</sub> C <sub>6</sub> H <sub>5</sub> )
249	CH <sub>3</sub> COCH <sub>2</sub> -	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	gum	Rf 0.2 (silica; CH <sub>2</sub> Cl <sub>2</sub> , CH <sub>3</sub> OH 95:5)

Example No.	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
250	$C_6H_5CH_2-N$ 	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	gum	RE 0.4 (silica; CH <sub>2</sub> Cl <sub>2</sub> , CH <sub>3</sub> OH, CH <sub>3</sub> CO <sub>2</sub> H 90:10:1)
251		4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	gum	RE 0.6 (silica; CH <sub>2</sub> Cl <sub>2</sub> , CH <sub>3</sub> OH, CH <sub>3</sub> CO <sub>2</sub> H 90:10:1)
252	CH <sub>3</sub> -C≡C-CH <sub>2</sub> -	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	Solid m.p. 126-128°C	71.38 7.83 3.05 (71.49 7.78 3.09)
253		4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	gum	72.03 8.29 2.81 (72.32 8.16 2.91)
254		4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	oil	71.29 7.69 2.64 (71.38 7.54 2.69)

Example No.	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Isolated Form	Analysis: Z (Theoretical in brackets) C H N
255		4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	oil (0.2 H <sub>2</sub> O)	68.78 7.96 2.86 (68.74 8.12 2.86)
256		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam (trifluoroacetate salt)	60.04 7.31 4.94 (59.37 7.04 4.78)
257		3-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	oil (hydrochloride salt)	RF 0.25 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> 1:9)
258		4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	RF 0.15 (silica; CH <sub>2</sub> Cl <sub>2</sub> , CH <sub>3</sub> OH, CH <sub>3</sub> CO <sub>2</sub> H 95:5:0.5)
259		4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	RF 0.10 (silica; CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> )

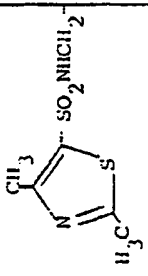
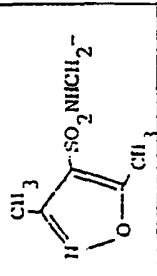
Example No.	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Isolated Form	Analysis, % (Theoretical in brackets) C H N
260		4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	Rf 0.5 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> 1:9)
261	CF <sub>3</sub> CO <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> - (1)	4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	foam	60.96 6.79 2.36 (61.15 6.72 2.46)
262	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CONH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	Rf 0.25 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> , 10:90)
263	C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub> NH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	solid m.p. 175-177°C	58.16 6.98 5.60 (58.28 6.93 5.67)
264	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CONH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	Rf. 0.45 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> , 10:90)
265	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NHCONH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	Rf 0.3 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> 10:90)

(1) Using enter of Example 214

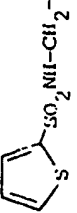
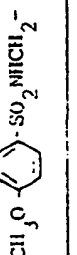
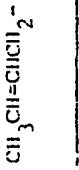
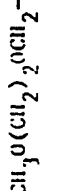

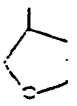


Example No.	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
266	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub> NH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	solid m.p. 159-162°C	55.02 8.13 5.89 (54.76 7.88 6.08)
267	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SO <sub>2</sub> NH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	white solid m.p. 161-164°C	59.12 7.13 5.69 (59.03 7.13 5.51)
268	$\begin{array}{c} \text{CH}_2\text{CH}_3 \\   \\ \text{C}_6\text{H}_5\text{CH}_2\text{CONCH}_2- \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil (0.1 CH <sub>2</sub> Cl <sub>2</sub> )	64.30 8.02 5.10 (64.82 7.89 5.20)
269	$\begin{array}{c} \text{CH}_2\text{CH}_3 \\   \\ \text{C}_6\text{H}_4\text{CONCH}_2- \end{array}$ 	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	RF 0.4 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> 10:90)
270	$\begin{array}{c} \text{CH}_2\text{CH}_3 \\   \\ \text{CH}_3\text{SO}_2\text{NCH}_2- \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	RF. 0.45 (silica; CH <sub>3</sub> OH, CH <sub>2</sub> Cl <sub>2</sub> 10:90)

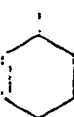


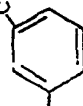
Example No.	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
271	$\begin{array}{c} \text{CH}_3 \\   \\ \text{C}_6\text{H}_5\text{CH}_2\text{OCNH-CHCH}_2- \\ \text{Diastereomer A} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil (1.0 H <sub>2</sub> O)	63.44 7.79 4.47 (63.48 8.08 5.11)
272	$\begin{array}{c} \text{CH}_3 \\   \\ \text{C}_6\text{H}_5\text{CH}_2\text{OCNH-CHCH}_2- \\ \text{Diastereomer B} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	gum (0.75 H <sub>2</sub> O)	64.29 7.79 4.62 (64.00 8.06 5.15)
273	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3\text{OCNH-CHCH}_2- \\ \text{Diastereomer A} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	60.94 8.49 5.97 (60.77 8.43 6.17)
274	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3\text{OCNH-CHCH}_2- \\ \text{Diastereomer B} \end{array}$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	Ref 0.3 (silica; CH <sub>3</sub> OH:CH <sub>2</sub> Cl <sub>2</sub> 5:95)

Example No.	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
275	$C_6H_5CH_2OC(=O)NH-CH(CH_2CH_3)-$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	65.25 7.40 4.77 (65.63 7.98 5.28)
276	$C_6H_5CONHCH_2-$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	solid m.p. 167-168°C	66.08 7.77 5.73 (66.08 7.68 5.93)
277	$CH_3CONHCH_2-$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	61.71 8.57 6.73 (61.44 8.35 6.83)
278	$CH_3(CH_2)_2SO_2NHCH_2-$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam (0.5 H <sub>2</sub> O)	54.66 8.03 5.73 (54.64 8.13 5.79)
279	$C_6H_5SO_2NHCH_2-$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam (1.0 H <sub>2</sub> O)	57.16 6.98 5.34 (57.02 7.27 5.31)
280	$CH_3CH_2SO_2CH_2-$	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	gum	56.61 8.13 2.87 (56.60 7.92 3.14)
281	$NH_2CH_2-$	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	Rf 0.4 (silica; CH <sub>2</sub> Cl <sub>2</sub> , CH <sub>3</sub> OH, CH <sub>3</sub> CO <sub>2</sub> H, 80:20:1)

Example No.	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
282	CF <sub>3</sub> SO <sub>2</sub> NH-	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	solid m.p. 117°C	46.77 6.36 5.56 (46.90 6.01 5.76)
283	CF <sub>3</sub> SO <sub>2</sub> NHCH <sub>2</sub> -	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	solid m.p. 176-177°C	47.62 5.96 5.59 (47.99 6.24 5.60)
284	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub> NH-	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	54.22 7.94 5.93 (54.76 7.88 6.08)
285	C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub> NHCH <sub>2</sub> -	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam (0.25 H <sub>2</sub> O)	58.73 6.89 5.50 (58.51 7.17 5.46)
286		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	53.08 6.96 7.60 (53.02 6.86 7.73)
287		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	54.43 7.06 8.44 (54.63 7.07 7.96)
288	C <sub>6</sub> H <sub>5</sub> CONHCH <sub>2</sub> -	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam (0.375 H <sub>2</sub> O)	65.02 7.67 5.43 (65.14 7.67 5.84)



Example No.	R <sup>S</sup>	-CO <sub>2</sub> R <sup>4</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
289		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam (0.375 H <sub>2</sub> O)	52.91 6.39 5.28 (52.97 6.72 5.39)
290		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	58.24 7.08 5.22 (57.97 7.11 5.20)
291		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam (0.25 H <sub>2</sub> O)	66.18 8.67 3.66 (66.38 8.99 3.52)
292		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	62.19 9.00 3.32 (61.80 8.72 3.28)
293		3-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	foam	67.55 8.71 2.73 (68.23 8.68 2.57)
294		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	64.07 8.77 3.79 (64.52 8.62 3.42)
295		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam (0.5 H <sub>2</sub> O)	65.80 8.35 3.80 (65.97 8.56 3.50)
296		3-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	glass (0.6 H <sub>2</sub> O)	69.86 7.55 3.25 (69.83 7.86 3.02)

Example No.	R <sup>5</sup>	-CO <sub>2</sub> R <sup>4</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
297		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	foam	68.00 8.89 3.43 (68.71 8.89 3.34)
298		3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	67.25 9.01 3.27 (67.78 9.15 3.43)
299	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>4</sub> -	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	Rf. 0.18 (silica; CH <sub>2</sub> Cl <sub>2</sub> , ether 1:1)
300	CH <sub>2</sub> =CH-CH <sub>2</sub> -	3-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	oil	66.08 8.76 3.56 (66.46 8.76 3.69)
301		4-CO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	gum	68.05 7.56 3.08 (68.76 7.91 2.97)
302	CH <sub>3</sub> NHCO- 	4-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	0.125 CH <sub>2</sub> Cl <sub>2</sub>	65.76 8.07 5.62 (65.52 7.75 5.64)

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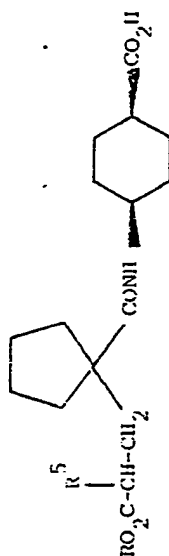
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Example No.	R <sup>5</sup>	R	Isolated Form	Analysis % (Theoretical in Brackets) C H N
309	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	gum (0.5 H <sub>2</sub> O)	66.53 8.03 2.98 (66.60 8.38 2.99)
310	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	(0.5 H <sub>2</sub> O)	69.13 8.37 2.86 (69.00 8.46 3.10)
311	CH <sub>3</sub> C≡CCH <sub>2</sub> -	C <sub>2</sub> H <sub>5</sub> -	gum	66.87 8.75 3.56 (67.49 8.49 3.58)
312	CH <sub>3</sub> C≡CCH <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	solid m.p. 107-10°C (0.5 H <sub>2</sub> O)	70.28 7.74 3.03 (70.10 7.85 3.03)
313	CH <sub>2</sub> =CHCH <sub>2</sub> -	C <sub>2</sub> H <sub>5</sub> -	solid m.p. 111-113°C	66.20 8.78 3.49 (66.46 8.76 3.69)
314		C <sub>2</sub> H <sub>5</sub> -	foam (0.75 H <sub>2</sub> O)	66.62 8.87 3.32 (66.56 8.96 3.23)

55 **EXAMPLE 315**

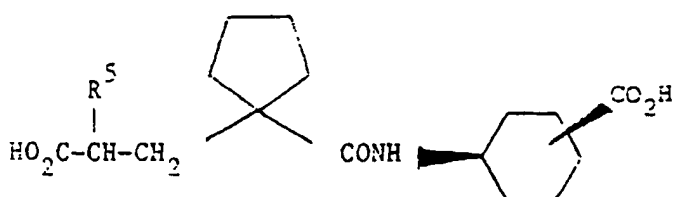
3-{1-[(cis-4-Carboxy-cyclohexyl)carbamoyl]cyclopentyl}-2-(methoxymethyl)propanoic acid

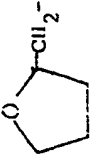
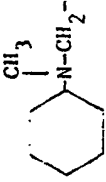
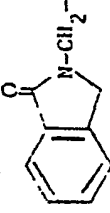
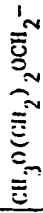
3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(methoxymethyl)propanoic acid

(390 mg, 0.88 mmole) was dissolved in tetrahydrofuran (25 ml) and water (10 ml) and was stirred with 5% palladium on carbon catalyst (100 mg) under an atmosphere of hydrogen at 50 p.s.i. (3.45 bar) for 3.5 hours. The catalyst was removed by filtration and the solvent evaporated to give a yellow gum. The residue was taken up in ethyl acetate (50 ml), and extracted into saturated sodium hydrogen carbonate solution (3 x 20 ml). The aqueous layer was separated, acidified with 2N hydrochloric acid and extracted with ethyl acetate (2 x 50 ml). The organic layer was separated, dried over magnesium sulphate, the solvent evaporated and the residue azeotroped with dichloromethane to give the title products as a colourless foam (264 mg, 85%). Found: C,59.02; H,7.89; N,3.73.  $C_{18}H_{29}NO_6 \cdot 0.15 CH_2Cl_2$  requires C,59.21; H,8.02; N,3.80%.

#### 10 EXAMPLES 316 - 321

The following Examples were prepared by the procedure of Example 315 starting with the appropriate ester. The products are cis-3- and cis-4- cyclohexane carboxylic acids.



Example No.	R <sup>5</sup>	-CO <sub>2</sub> H	Isolated Form	Analysis % (Theoretical in brackets) C H N
316		4-CO <sub>2</sub> H	foam (0.25 H <sub>2</sub> O)	62.99 8.53 3.44 (63.05 8.44 3.50)
317		3-CO <sub>2</sub> H	foam (hydrochloride)	61.37 8.92 5.94 (60.94 8.74 5.91)
318		4-CO <sub>2</sub> H	foam (1.25 H <sub>2</sub> O)	62.68 7.21 5.34 (62.68 7.26 5.84)
319		3-CO <sub>2</sub> H	foam (0.5 H <sub>2</sub> O)	59.05 8.33 3.51 (58.80 8.39 3.43)

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Example No.	R <sup>5</sup>	-CO <sub>2</sub> H	Isolated Form	Analysis % (Theoretical in brackets) C H N
320	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> -	4-CO <sub>2</sub> H	foam	64.59 8.50 3.05 (64.20 8.84 3.00)
321	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	4-CO <sub>2</sub> H	Solid m.p. 164-165°C (0.75 H <sub>2</sub> O)	66.61 7.56 3.57 (66.56 7.90 3.38)

**EXAMPLE 322**

55 3-{1-[(cis-4-Ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(cyclohexyl)propanoic acid

3-{1-[(cis-4-Ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(cyclohex-2-enyl)propanoic acid (185 mg, 0.441 mmol) was dissolved in absolute ethanol (50 ml) and hydrogenated at 50 p.s.i. (3.45 bar) over

5% palladium on charcoal (10 mg) as catalyst. The solution was filtered and the solvent evaporated to give the title compound as a colourless gum (180 mg, 97%). Found: C,65.56; H,9.05; N,3.31.  $C_{24}H_{33}NO_5 \cdot H_2O$  requires C,65.57; H,9.39; N,3.18%.

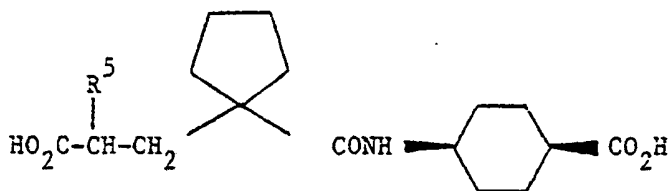
#### 5 EXAMPLE 323

3-{1-[(cis-4-Carboxy-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-ethoxyethyl)propanoic acid

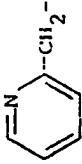
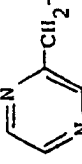
3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-ethoxyethyl)propanoic acid (225 mg, 0.476 mmole) was dissolved in 1,4-dioxan (20 ml), ethanol (4 ml) and water (6 ml) and was treated with 10 1N sodium hydroxide solution (2.4 ml, 2.4 mmole). After 20 hours at room temperature, the solution was evaporated to half volume, diluted with water (20 ml) and washed with diethyl ether. The aqueous layer was separated, acidified with 2N hydrochloric acid and extracted with ethyl acetate (3 x 20 ml). The ethyl acetate layer was separated, dried over magnesium sulphate and the solvent evaporated to give the title product as a colourless foam (161 mg, 88%). Found: C,61.89; H,8.29; N,3.62.  $C_{20}H_{33}NO_6 \cdot 0.2 H_2O$  requires 15 C,62.06; H,8.69; N,3.62%.

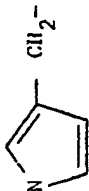
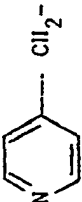
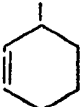
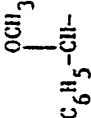
#### EXAMPLES 324 - 391

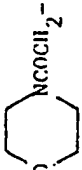
The following Examples were prepared by the procedure of Example 323 starting with the appropriate 20 ester:





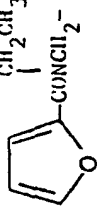
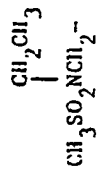
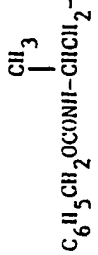
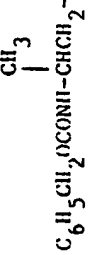
Example No.	R <sup>5</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
324	$\text{CH}_3\text{O}(\text{CH}_2)_3^-$	foam (0.3 H <sub>2</sub> O)	61.78 8.50 3.51 (61.77 8.71 3.60)
325	$\text{CH}_3\text{O}(\text{CH}_2)_2\text{OCH}_2^-$	white solid m.p. 117-9°C	60.23 8.46 3.31 (60.13 8.33 3.51)
326		foam (0.75 H <sub>2</sub> O)	63.43 7.32 6.47 (63.52 7.63 6.74)
327		foam (0.7 H <sub>2</sub> O)	60.90 7.51 10.30 (60.70 7.36 10.11)
328	$\text{CH}_2=\text{CH}-\text{CH}_2^-$	foam (0.25 H <sub>2</sub> O)	64.14 8.52 4.13 (64.11 8.35 3.94)
329	$\text{CH}_3\text{COCCH}_2^-$	foam (0.12 CH <sub>2</sub> Cl <sub>2</sub> )	60.77 7.99 3.31 (60.81 7.81 3.71)

Example No.	R <sup>5</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
330	$\text{C}_6\text{H}_5\text{CH}_2\text{N}-$ 	foam (3 H <sub>2</sub> O)	60.71 6.65 7.88 (60.54 7.72 7.85)
331		foam (0.5 H <sub>2</sub> O) (0.3 CH <sub>2</sub> Cl <sub>2</sub> )	60.67 7.05 6.33 (60.99 7.26 6.37)
332	$\text{CH}_3\text{C}\equiv\text{C}-\text{CH}_2-$	solid, m.p. 196-8°C	65.98 8.13 3.98 (66.09 8.04 3.85)
333		solid (0.2 H <sub>2</sub> O)	66.85 8.51 3.43 (66.88 8.52 3.55)
334		solid, m.p. 167-8°C	66.75 7.77 3.10 (66.80 7.71 3.25)

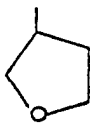
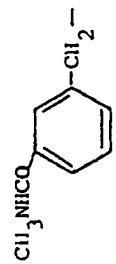
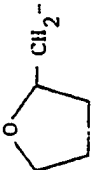
Example No.	R <sup>5</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
335	$\text{C}_6\text{H}_5\text{CH}_2\text{-N(CH}_3)_2$	foam (0.5 H <sub>2</sub> O)	66.65 7.97 7.09 (66.20 8.22 6.18)
336	$\text{CH}_3\text{O(CH}_2)_2\text{NHCOCCH}_2$	foam (0.5 H <sub>2</sub> O, 0.1 CH <sub>2</sub> Cl <sub>2</sub> )	57.38 8.15 5.94 (57.08 7.99 6.31)
337		foam (0.3 CH <sub>2</sub> Cl <sub>2</sub> )	58.05 8.04 5.60 (57.73 7.51 6.04)
338	$\text{CH}_3\text{SO}_2(\text{CH}_2)_2$	foam (1.5 H <sub>2</sub> O)	51.37 7.55 2.72 (51.34 7.21 3.15)
339	$110(\text{CH}_2)_4(1)$	foam (0.5 H <sub>2</sub> O)	61.05 8.57 3.46 (61.20 8.73 3.57)


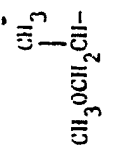
(1) using ester of Example 261

Example No.	R <sup>5</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
340	$C_6H_5CH_2OCONH-$	white solid m.p. 158-162°C (0.1 CH <sub>2</sub> Cl <sub>2</sub> 0.25 H <sub>2</sub> O)	61.16 7.07 5.87 (61.13 6.96 5.92)
341	$C_6H_5SO_2NH-$	white solid m.p. 211-213°C	56.86 6.50 5.99 (56.63 6.48 6.01)
342	$C_6H_5CH_2CONH-$	white solid m.p. 177-180°C	65.22 7.38 6.21 (64.84 7.26 6.30)
343	$C_6H_5CH_2NHCONH-$	white solid m.p. 176-180°C (1.25 H <sub>2</sub> O)	59.98 7.18 8.55 (59.80 7.42 8.72)
344	$CH_3(CH_2)_2SO_2NH-$	white solid	52.49 7.57 6.29 (52.76 7.46 6.48)
345	$C_6H_5CH_2SO_2NH-$	white solid m.p. 187-191°C	57.27 6.94 5.66 (57.48 6.71 5.83)
346	$C_6H_5CH_2OCONCH_2-$ $\quad \quad \quad  $ $\quad \quad \quad CH_2CH_3$	foam	64.48 7.65 5.49 (64.52 7.62 5.58)

Example No.	R <sup>5</sup>	Isolated Form	Analysts % (Theoretical in brackets) C H N
347		foam (0.125 CH <sub>2</sub> Cl <sub>2</sub> )	61.48 7.31 5.98 (61.24 7.30 5.92)
348		foam (0.2 CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> )	53.40 7.69 5.86 (53.79 7.67 6.27)
349	 Diastereomer A	foam (0.1 CH <sub>2</sub> Cl <sub>2</sub> 0.5 H <sub>2</sub> O)	62.69 7.58 5.11 (62.58 7.60 5.39)
350	 Diastereomer B	foam (0.6 H <sub>2</sub> O)	62.88 7.45 5.26 (63.16 7.70 5.46)

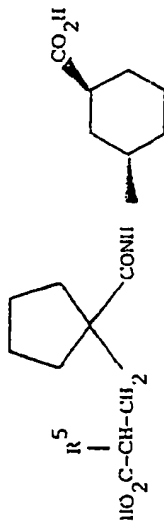
Example No.	R <sup>S</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
351	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3\text{OCONH}-\text{CHCH}_2- \\ \text{Diastereomer A} \end{array}$	foam (0.25 CH <sub>2</sub> Cl <sub>2</sub> )	57.06 8.23 5.81 (57.00 7.77 6.26)
352	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3\text{OCONH}-\text{CHCH}_2- \\ \text{Diastereomer B} \end{array}$	foam (0.25 CH <sub>2</sub> Cl <sub>2</sub> )	57.09 7.89 6.15 (57.00 7.77 6.26)
353	$\begin{array}{c} \text{CH}_2\text{CH}_3 \\   \\ \text{C}_6\text{H}_5\text{CH}_2\text{OCONH}-\text{CH}- \end{array}$	foam (0.1 CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> , 1.0 H <sub>2</sub> O)	62.48 7.56 5.06 (62.16 7.77 5.29)
354	C <sub>6</sub> H <sub>5</sub> CONHCH <sub>2</sub> -	solid m.p. 89-93°C (0.16 CH <sub>2</sub> Cl <sub>2</sub> 0.08 CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> 0.4 H <sub>2</sub> O)	62.05 7.38 6.85 (62.18 7.20 5.92)
355	CH <sub>3</sub> CONHCH <sub>2</sub> -	solid m.p. 51-53°C (0.1 CH <sub>2</sub> Cl <sub>2</sub> 0.5 CH <sub>3</sub> CO <sub>2</sub> H)	57.17 8.24 6.98 (57.34 7.71 6.61)

Example No.	R <sup>S</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
356	$\text{CH}_3(\text{CH}_2)_2\text{SO}_2\text{NHCCH}_2^-$	foam (0.1 $\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$ 0.5 $\text{H}_2\text{O}$ )	52.73 8.01 6.13 (52.76 7.77 6.03)
357	$\text{C}_6\text{H}_5\text{SO}_2\text{NHCCH}_2^-$	foam (1.0 $\text{H}_2\text{O}$ )	55.70 6.77 5.51 (55.41 6.87 5.62)
358	$\text{CH}_3\text{CH}_2\text{SO}_2\text{CH}_2^-$	foam (0.2 $\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$ )	54.44 7.68 1.14 (54.65 7.55 3.22)
359	$\text{CF}_3\text{SO}_2\text{NH}-$	foam (0.375 $\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$ )	45.78 6.15 5.58 (45.69 5.96 5.76)
360		foam	62.59 8.01 3.71 (62.97 8.19 3.62)
361		foam	63.17 7.31 5.47 (63.21 7.25 5.84)
362		foam (0.25 $\text{CH}_3\text{CO}_2\text{H}$ )	61.90 8.16 3.38 (62.10 8.14 3.53)


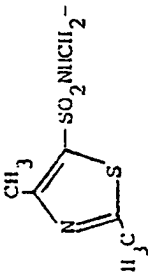
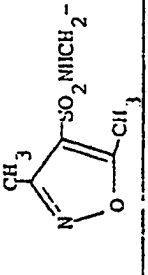
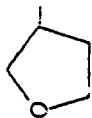
Example No.	R <sup>5</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
363		foam (H <sub>2</sub> O, 0.15 CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> )	58.38 8.00 3.07 (58.88 8.35 3.18)
364		foam (0.25 H <sub>2</sub> O)	62.01 9.11 3.39 (61.91 8.70 3.61)

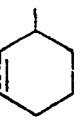
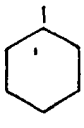

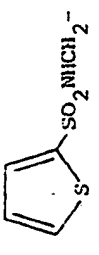
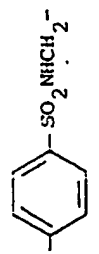


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Example No.	R <sup>5</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
365	Nil-CH <sub>2</sub> -	solid m.p. 197-200°C (0.5 H <sub>2</sub> O)	58.65 8.53 7.87 (58.43 8.37 8.02)
366	CF <sub>3</sub> SO <sub>2</sub> Nil-CH <sub>2</sub> -	solid m.p. 107-109°C	45.73 5.62 5.69 (45.75 5.76 5.93)
367	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub> Nil-	solid m.p. 163-165°C	52.90 7.72 6.26 (52.76 7.66 6.48)
368	C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub> Nil-CH <sub>2</sub> -	foam (1.0 H <sub>2</sub> O; 0.5 CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> )	55.74 6.71 5.61 (55.33 7.06 5.16)

Example No.	R <sup>5</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
369	$C_6H_5CONHCH_2^-$	foam (0.5 H <sub>2</sub> O)	63.58 7.49 5.71 (63.56 7.33 6.18)
370		solid	64.38 8.88 3.58 (65.72 8.55 3.83)
371		foam (0.25 CH <sub>2</sub> Cl <sub>2</sub> )	49.56 6.39 7.45 (49.77 6.29 7.83)
372		foam (0.25 CH <sub>2</sub> Cl <sub>2</sub> )	51.09 6.40 7.88 (51.31 6.48 8.08)
373	$CH_3CH=CHCH_2^-$	gum	65.86 8.52 3.84 (65.73 8.55 3.83)
374		foam (0.5 H <sub>2</sub> O)	61.24 8.22 3.40 (61.52 8.26 3.58)
375	$CH_3C\equiv CCH_2^-$	foam (0.5 H <sub>2</sub> O, 0.1 CH <sub>2</sub> Cl <sub>2</sub> , 0.1 <sup>2</sup> CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> )	63.13 8.37 4.02 (63.17 8.02 3.67)

Example No.	R <sup>5</sup>	Isolated Form	Analysis % (Theoretical in brackets) C H N
376		foam (0.2 CH <sub>2</sub> Cl <sub>2</sub> )	65.56 8.42 3.52 (65.75 8.30 3.45)
377		foam (0.5 H <sub>2</sub> O)	66.24 8.92 3.14 (66.30 9.10 3.51)
378		foam (0.06 CH <sub>2</sub> Cl <sub>2</sub> )	64.89 8.51 3.53 (65.78 8.68 3.64)
379	CH <sub>2</sub> =CHCH <sub>2</sub> -	foam	63.95 8.17 3.99 (64.11 8.35 3.94)
380		foam (0.5 H <sub>2</sub> O)	50.76 6.28 5.46 (50.89 6.31 5.65)
381		foam	56.69 6.95 5.10 (56.46 6.71 5.49)

EXAMPLE 382  
 3-{1-[(cis-3-Ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(4-hydroxybutyl)propanoic acid, calcium salt

3-{1-[(cis-3-Ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(4-benzyloxybutyl)propanoic acid (742 mg, 1.48 mmole) was dissolved in absolute ethanol (10 ml) containing 10% palladium on carbon (74 mg) as catalyst, and the mixture hydrogenated at 50 p.s.i. (3.45 bar) for 20 hours at room temperature. Further catalyst (70 mg) was added and the mixture hydrogenated for a further 4.5 hours under the same conditions.

5 The solution was filtered, the solvent evaporated under vacuum and the residue azeotroped six times with dichloromethane. The crude product was taken up in ethyl acetate (50 ml) and extracted into saturated sodium bicarbonate solution (2 x 50 ml). The aqueous extract was acidified to pH 1 with 2N hydrochloric acid and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and the solvent evaporated to yield the title acid as a colourless foam (556 mg, 92%). This product was dissolved in ethanol (15 ml) and a suspension of calcium hydroxide (71 mg) in water (3 ml) was added. The mixture was stirred at 30 °C for 45 minutes then filtered and evaporated. The residue was dissolved in dichloromethane, dried over MgSO<sub>4</sub>, filtered and the solvent evaporated. The residue was triturated with diethyl ether and dried under vacuum at 70 °C for 2 days to give the calcium salt as a white solid, m.p. 116-120 °C. Found: C,61.30; H,8.32; N,3.61. C<sub>44</sub>H<sub>72</sub>N<sub>2</sub>O<sub>12</sub>Ca requires C,61.37; H,8.43; N,3.25%.

#### EXAMPLE 383

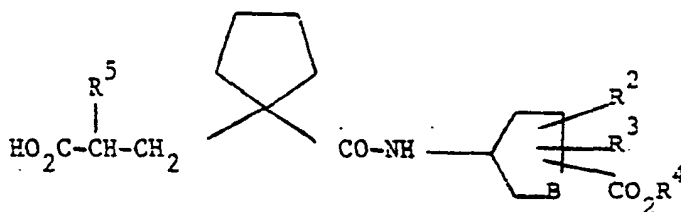
3-[[1-(cis-5-Carboxy-cis-2-methyl-cyclohexyl)carbamoyl]cyclopentyl]-2-(2-methoxyethyl)propanoic acid

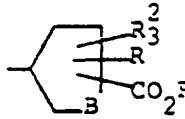
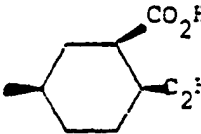
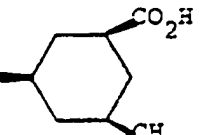
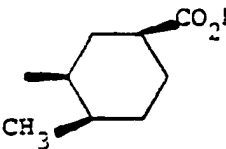
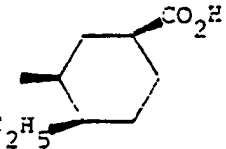
20 3-[[1-(cis-5-Methoxycarbonyl-cis-2-methyl-cyclohexyl)carbamoyl]cyclopentyl]-2-(2-methoxyethyl)propanoic acid benzyl ester (630 mg, 1.29 mmole) in ethanol (20 ml) and water (15 ml) was hydrogenated at room temperature for three hours over 5% palladium on charcoal catalyst (200 mg) at 50 p.s.i. (3.45 bar) pressure. The suspension was filtered through a short Avicel column and the solvent evaporated under reduced pressure. The mono-ester (490 mg), which was obtained as a gum was dissolved in 1N sodium hydroxide (5 ml) and the solution washed with ether. The ether washings were extracted with water and the combined aqueous solutions evaporated to 5 ml at 40 °C, under reduced pressure and then allowed to stand at room temperature overnight.

25 The resulting clear solution was acidified with 2N hydrochloric acid and extracted with methylene chloride. The organic extract was washed with water, dried (MgSO<sub>4</sub>), and evaporated to give the required diacid as a foam (411 mg, 83%). Found: C,61.95; H,8.58; N,3.69. C<sub>20</sub>H<sub>33</sub>NO<sub>6</sub>·0.25 H<sub>2</sub>O requires C,61.91; H,8.70; N,3.61%.

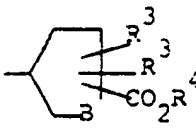
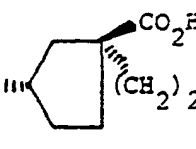
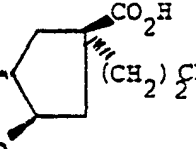
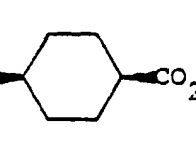
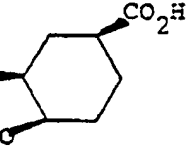
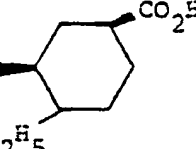
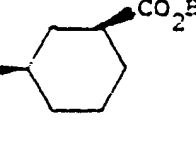
#### EXAMPLES 384-393

35 The following Examples were prepared by the procedure of Example 383 starting with the appropriate ester of formula (V) wherein R<sup>13</sup> is benzyl and R<sup>14</sup> is methyl or ethyl.



Example No.	$R^5$		Analysis % (Theoretical in brackets) C            H            N		
384	$CH_3(CH_2)_2-$		66.06 (66.11)	9.18 9.25	3.62 3.67
385	$CH_3(CH_2)_2-$		65.36 (65.37)	9.09 9.05	3.78 3.81
386	$CH_3(CH_2)_2-$		65.10 (65.37)	9.14 9.05	3.55 3.81
387	$CH_3O-(CH_2)_2-$		62.02 (62.04)	8.60 8.73	3.38 3.45 (1)

(1) 0.5 hydrate.

Example No.	$R^5$		Analysis % (Theoretical in brackets) C H N		
389	$CH_3O-(CH_2)_2-$		63.21 (63.45)	9.00 8.87	3.35 3.52
389	$CH_3O-(CH_2)_2-$		60.03 (59.68)	8.78 8.59	3.16 3.32
390	$CH_3O(CH_2)_2-$		57.89 (57.85)	8.30 8.18	3.16 3.55
391	$CH_3O(CH_2)_2-$		57.23 (57.23)	8.09 8.10	3.35 3.50) (1)
392	$CH_3(CH_2)_2-$		64.86 (66.11)	9.21 9.25	3.37 3.67)
393	$HO(CH_2)_4-$		60.41 (60.37)	8.39 8.76	3.30 3.52) (2)

(1) hemihydrate

(2) 0.8 H<sub>2</sub>O**EXAMPLE 394**2-(4-Aminobutyl)-3-{1-[cis-4-carboxy-cyclohexyl]carbamoyl}cyclopentyl}propanoic acid t-butyl ester

2-(4-Azidobutyl)-3-{1-[cis-4-benzyloxycarbonylcyclohexyl]carbamoyl}cyclopentyl}propanoic acid t-butylester (2.73 g, 5.11 mmole) in tetrahydrofuran (150 ml) and water (75 ml) was stirred with 5% palladium on carbon catalyst (250 mg) at room temperature under hydrogen at 50 p.s.i. (3.45 bar) for 2.5 hours. After

this time the catalyst was removed by filtration, the solvent evaporated and the residue triturated with diethyl ether (3 x 50 ml) to give the title product as a colourless solid (1.45 g, 65%) m.p. 186-90 °C (with decomposition). Found: C,64.80; H,9.69; N,5.92.  $C_{24}H_{42}N_2O_5 \cdot 0.33 H_2O$  requires C,64.83; H,9.67; N,6.30%.

5 **EXAMPLE 395**

2-(4-Acetamidobutyl)-3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester

2-(4-Aminobutyl)-3-{1-[(cis-4-carboxy-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester (280 mg, 0.64 mmole) was dissolved in dichloromethane (30 ml) and treated with triethylamine (152 mg, 1.51 mmole) and acetic anhydride (78 mg, 0.76 mmole). After 20 minutes at room temperature the solvent was evaporated and the residue was dissolved in ethyl acetate (50 ml), washed with 1N hydrochloric acid (50 ml) and water (2 x 50 ml). The organic layer was separated, dried over magnesium sulphate and evaporated to give a colourless foam. Chromatography on silica gel eluting with a mixture of methanol and dichloromethane (1:19 - 1:4 by volume) and evaporation of the appropriate fractions gave the title product as a colourless foam (273 mg, 89%). Found: C,60.09; H,8.68; N,4.99.  $C_{25}H_{44}N_2O_5 \cdot 0.6 CH_2Cl_2$  requires, C,60.10; H,8.57; N, 5.27%.

**EXAMPLE 396**

2-(4-Aminobutyl)-3-{1-[(cis-4-carboxy-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid

20 2-(4-Aminobutyl)-3-{1-[(cis-4-carboxy-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester (1.0 g, 2.28 mmole) was dissolved in trifluoroacetic acid (8 ml) at 0 °C. After 3 days at this temperature the solvent was evaporated and the residue azeotroped with dichloromethane (3 x 50 ml). The resulting brown oil was purified by passage through ion exchange resin (Bio-Rad AG 50W-X8, 30 ml) eluting with pyridine and water (3:100 by volume), and the appropriate fractions evaporated to give the title product as a colourless foam (700 mg, 80%). Found: C,61.97; H,9.08; N,7.69.  $C_{20}H_{34}N_2O_5 \cdot 0.1 C_5H_5N \cdot 0.3 H_2O$  requires C,62.21; H,8.94; N,7.43%.

**EXAMPLE 397**

30 2-(4-Acetamidobutyl)-3-{1-[(cis-4-carboxy-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid

2-(4-Acetamidobutyl)-3-{1-[(cis-4-carboxy-cyclohexyl)carbamoyl]cyclopentyl}propanoic acid t-butyl ester (270 mg, 0.58 mmole) was dissolved in trifluoroacetic acid (4 ml) at 0 °C. After 20 hours the solvent was evaporated and the resulting oil azeotroped with dichloromethane (3 x 20 ml). The oil was taken up in ethyl acetate (20 ml) and washed with water (7 x 20 ml) until the washings were neutral. The organic layer was separated, dried over magnesium sulphate, and evaporated. The residue was dissolved in saturated sodium carbonate solution (20 ml) washed with ethyl acetate (2 x 20 ml), acidified with 2N hydrochloric acid and then extracted with ethyl acetate (3 x 20 ml). The organic layer was separated, dried over magnesium sulphate and evaporated. The residue was azeotroped with tetrahydrofuran to give the title product as a colourless foam (110 mg, 45%). Found: C,62.58; H,8.71; N,5.27.  $C_{22}H_{36}N_2O_5 \cdot C_4H_8O$  requires C,62.88; H,8.93; N,5.64%.

**EXAMPLE 398**

3-{1-[(cis-4-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(imidazo-2-ylmethyl)propanoic acid

45 3-{1-[(cis-4-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(1-benzyl-imidazol-2-yl-methyl)propanoic acid (Example 147) (800 mg, 1.5 mmole) in aqueous ethanol (80 ml, 1:1 by volume) was hydrogenated for seven hours at 30 p.s.i. (2 bar) pressure over 5% palladium on charcoal (400 mg). The catalyst was removed by filtration and the solvent evaporated under reduced pressure. The product was dissolved in 1N sodium hydroxide (6 ml), and taken up on cation exchange resin (Dow, AG 50W-X8). Elution with aqueous pyridine, increasing in concentration from 0 to 5%, and evaporation of the eluent gave the title diacid as a white foam (270 mg, 34%). Found: C,58.76; H,7.50; N,10.18.  $C_{20}H_{29}N_3O_5 \cdot H_2O$  requires C,58.66; H,7.63; N,10.26%.

**EXAMPLE 399**

55 3-{1-[(cis-4-Carboxycyclohexyl)-carbamoyl]cyclopentyl}-2-[2-(2-thiazolylcarbamoyl)ethyl]propanoic acid

3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)-carbamoyl]cyclopentyl}-2-[2-(2-thiazolylcarbamoyl)ethyl]-propanoic acid benzyl ester (120 mg, 0.18 mmole) and anisole (121 mg, 1.1 mmole) were dissolved in

dichloromethane (2.5 ml). A solution of aluminium chloride (149 mg, 1.1 mmole) in nitromethane (2.5 ml) was added at 0 °C under nitrogen. After stirring for 16 hours at room temperature the mixture was poured into saturated aqueous sodium hydrogen carbonate, filtered and the aqueous filtrate acidified with dilute hydrochloric acid. The solution was saturated with solid sodium chloride and the product extracted under vacuum to yield the title compound (50 mg, 58%). Rf. 0.4 (silica; CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>3</sub>OH, CH<sub>3</sub>CO<sub>2</sub>H, 90:10:1).

## EXAMPLE 400

2-Amino-3-{1-[cis-4-carboxy-cyclohexyl]carbamoyl}cyclopentyl}propanoic acid

2-Benzyloxycarbonylamino-3-{1-[cis-4-carboxy-cyclohexyl]carbamoyl}cyclopentyl}propanoic acid (260 mg, 0.56 mmole) was dissolved in a mixture of ethanol (20 ml) and water (2 ml) and hydrogenated at 30 p.s.i. (2 bar) and room temperature for 3 hours. Filtration through Arbocell and evaporation of the solvent gave crude product which was dissolved in methanol, filtered and the filtrate evaporated. The residue was washed with dichloromethane and dried under vacuum to give the title compound as a cream-solid (33 mg, 18%). Found: C,55.72; H,8.00; N,7.65. C<sub>16</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>. 0.2 CH<sub>3</sub>OH. 1.0 H<sub>2</sub>O requires C,55.46; H,8.27; N,7.99%.

## EXAMPLE 401

3-{1-[cis-4-Carboxy-cyclohexyl]carbamoyl}-cyclopentyl}-2-[2-(hydroxy)ethoxymethyl]propanoic acid

3-{1-[cis-4-Carboxy-cyclohexyl]carbamoyl}-cyclopentyl}-2-[2-(methoxy)ethoxymethyl]propanoic acid (0.80 g, 2 mmole) was dissolved in dry dichloromethane (15 ml) and treated with trimethylsilyl iodide (1.4 ml, 10 mmole) at 0 °C under nitrogen. After 6 hours at 0 °C, the reaction was poured into ice-cold dilute sodium hydrogen carbonate and washed with dichloromethane. The aqueous phase was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 50 ml). The first extract contained starting material, the second and third extracts were combined, washed with dilute sodium thiosulphate, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give an orange oil. The residue was azeotroped with dichloromethane and washed with dichloromethane to give the title compound as a glassy foam (0.22 g, 29%). Found: C,57.24; H,8.07; N,3.42. C<sub>19</sub>H<sub>31</sub>NO<sub>7</sub>. 0.1 CH<sub>2</sub>Cl<sub>2</sub> 0.25 H<sub>2</sub>O requires C,57.58; H,8.02; N,3.52%.

## EXAMPLE 402

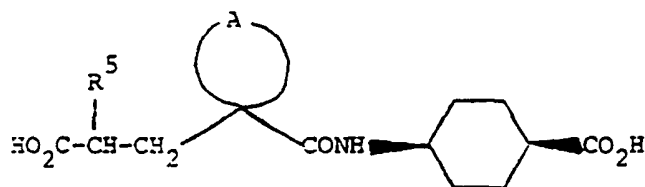
3-{1-[cis-4-Carboxycyclohexyl]carbamoyl}cyclopent-3-enyl}-2-propylpropanoic acid

Hexamethyldisilane (1.78 g, 12.19 mmole) and iodine (2.8g, 11.05 mmole) were heated at 65 °C with stirring under nitrogen for one hour. The mixture was cooled and cyclohexene (30 ml, 300 mmole) added followed by 3-{1-[cis-4-benzyloxycarbonylcyclohexyl] carbamoyl}cyclopent-3-enyl}-2-propylpropanoic acid benzyl ester (1.78 g, 3.35 mmole) in carbontetrachloride (30 ml) and the mixture was stirred at 65-70 °C, the progress of the reaction being followed by thin layer chromatography. After 18 hours trimethylsilyl iodide (2.0 g, 10.05 mmole) was added followed by a further addition (4.0 g, 20 mmole) 24 hours later. After a further 7 hours the mixture was cooled and poured onto a mixture of methylene chloride and water. The organic phase was washed with saturated brine and extracted with 0.1 N sodium hydroxide. The alkaline extract was washed with diethyl ether, acidified to pH 1-2 with concentrated hydrochloric acid and extracted with methylene chloride. The organic extract was washed with saturated brine, dried (MgSO<sub>4</sub>) and the solvent evaporated under vacuum to yield the title diacid as a yellow foam (1.05 g). Chromatography on silica gel, eluting with methylene chloride containing increasing proportions of methanol (1 to 5% by volume) gave the pure product as a pale yellow foam (650 mg, 55%). Found: C,62.69; H,8.11; N,3.99. C<sub>19</sub>H<sub>29</sub>NO<sub>5</sub>. 0.6 H<sub>2</sub>O requires C,62.99; H,8.40; N,3.87%.

EXAMPLES 403-405

The following compounds were prepared from the appropriate dibenzyl ester following the procedure of Example 402.





Example No	R <sup>5</sup>	A	Analysis % (Theoretical in brackets)		
			C	H	N
403	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -		61.40 (61.35)	8.03 7.99	3.78 3.77 <sup>(1)</sup>
404	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> -		63.15 (62.97)	8.36 8.19	3.60 3.67)
405			66.87 (61.09)	7.20 7.47	2.65 3.09)

(1) 0.25 H<sub>2</sub>O.

#### EXAMPLE 406

3-{1-[(cis-4-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid 1-(2,2-diethylbutyryloxy)ethyl ester

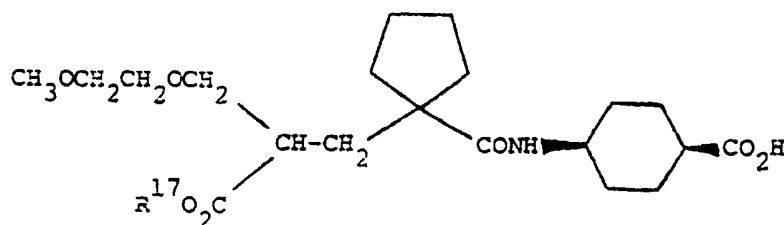
(a) 3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)-propanoic acid (0.5 g, 1.02 mmole) was dissolved in a mixture of acetonitrile (20 ml) and water (10 ml). A solution of caesium carbonate (1.0 g) in water (10 ml) was added dropwise until the pH of the solution was about 8. The resulting caesium salt solution was stirred at room temperature for 15 minutes and evaporated to dryness under vacuum. The residue was freed from water by azeotrope with toluene (3 x) then with acetonitrile (4 x). The resulting pale yellow foam was dissolved in dry dimethylformamide (40 ml) and a solution of 1-(2,2-diethylbutyryloxy)chloroethane (232 mg, 1.12 mmole) in dimethylformamide (1 ml) was added and the mixture stirred at room temperature overnight. The solvent was evaporated under reduced pressure and traces of dimethylformamide removed by azeotrope with toluene. The residue was dissolved in ethyl acetate (20 ml) and washed with 2M hydrochloric acid (3 x 20 ml). The

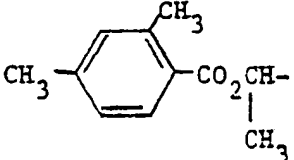
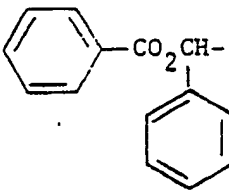
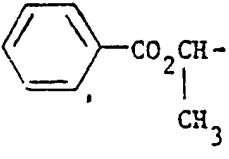
organic phase was dried over magnesium sulphate, the solvent evaporated under reduced pressure and the residue chromatographed on silica. Elution with a mixture of diethyl ether and dichloromethane (9:1) afforded the required diester as colourless gum (355 mg, 53%). Found: C, 67.53; H, 8.86; n, 2.23.  $C_{37}H_{57}NO_9$  requires C, 67.35; H, 8.71; N, 2.12%.

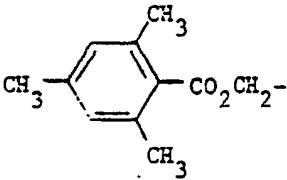
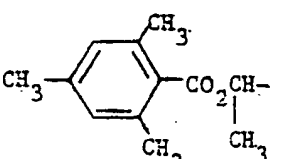
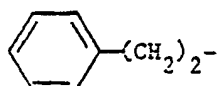
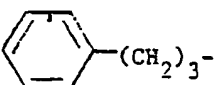
(b) The product from (a) above (318 mg, 0.482 mmole) was dissolved in a mixture of ethanol (27 ml) and water (3 ml) and hydrogenated at 50 p.s.i. (3.45 bar) over 10% palladium on charcoal catalyst (30 mg) for 4 hours. The reaction mixture was filtered and the solvent evaporated under vacuum. The residue was azeotroped with dichloromethane (4 x 50 ml) to afford the required compound as a white foam (275 mg, 100%). Found: C, 63.60; H, 9.22; N, 2.46.  $C_{30}H_{51}NO_9$  requires C, 63.24; H, 9.02; N, 2.46%.

#### EXAMPLES 407-418

The following compounds were prepared by the procedure of Example 406 by reaction of the caesium salt with the appropriate chloro compound. The products were obtained as foams or gums:



Example No.	$R^{17}$	Analysis % (Theoretical in brackets) C            H            N		
407	$(CH_3CH_2)_2CHCO_2CH_2-$	61.12 (61.46)	9.04 8.59	2.53 2.65)
408	$(CH_3CH_2)_2CHCO_2\underset{\begin{array}{c}   \\ CH_3 \end{array}}{CH}-$	61.92 (62.08)	9.41 8.75	2.47 2.59)
409		64.63 (64.67)	8.09 7.88	2.62 2.43)
410		67.08 (66.98)	7.25 7.11	2.04 2.30)
411		62.41 (62.57)	7.55 7.60	2.60 2.51)
412	$CH_3CH_2CO_2-\underset{\begin{array}{c}   \\ CH(CH_3)_2 \end{array}}{CH}-$	60.96 (60.46)	8.64 8.60	2.82 2.65)

Example No.	$R^{17}$	Analysis % (Theoretical in brackets) C            H            N		
413		64.54 (64.67)	7.90 7.88	2.31 2.43
414		63.68 (63.71)	7.86 8.11	2.20 2.32 (1)
415	$(CH_3)_3CCO_2CH_2-$	60.42 (60.80)	8.37 8.44	2.68 2.73
416		64.21 (64.47)	8.05 8.31	2.66 2.69 (2)
417		66.86 (67.28)	8.37 8.37	2.65 2.71
418	$CF_3CH_2-$	54.80 (54.87)	7.25 7.12	2.57 2.91

(1) 0.75 Hydrate (2) Monohydrate

## EXAMPLE 419

3-{1-[(cis-4-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid 1-naphthyl ester hemihydrate

(a) 2-(2-Methoxyethoxymethyl)-3-[(1-phenacyloxycarbonyl)cyclopentyl]propanoic acid t-butyl ester

Anhydrous potassium carbonate (18.8 g, 0.130 mole) was added to a stirred solution of phenacyl bromide (13.0 g, 0.0653 mole) and 3-(1-carboxycyclopentyl)-2-(2-methoxyethoxymethyl)propanoic acid t-butyl ester (21.34 g, 0.0645 mole) in dry dimethylformamide (100 ml). The resulting suspension was stirred at room temperature for 18 hours, then the bulk of the solvent was removed under vacuum and the residue partitioned between ethyl acetate (150 ml) and water (100 ml). The organic phase was separated, washed successively with water (50 ml), 1N hydrochloric acid (3 x 50 ml), and saturated aqueous sodium bicarbonate solution (50 ml), then dried over anhydrous magnesium sulphate. The solvent was removed by evaporation under vacuum to afford an oil which was purified by chromatography on silica gel eluting with a hexane-ethyl acetate gradient. The appropriate fractions were combined and the solvent evaporated under vacuum to give the title compound as a colourless oil (16.0 g, 55%), R<sub>f</sub> (silica) 0.71 (ethyl acetate/toluene, 1:1); 0.91 (diethyl ether).

15 (b) 2-(2-Methoxyethoxymethyl)-3-[(1-phenacyloxycarbonyl)cyclopentyl]propanoic acid

Dry trifluoroacetic acid (40 ml) was added dropwise over 20 minutes to a stirred solution of the previous product (8.0 g, 0.0178 moles) in dry methylene chloride (50 ml) at 0 °C. The cooling bath was then removed and stirred was continued for 3 hours, during which time the reaction mixture darkened considerably. Evaporation under vacuum provided a dark oil which was azeotroped with methylene chloride (3 x 50 ml), and dissolved in saturated aqueous sodium bicarbonate solution (100 ml). The resulting solution was washed with diethylether (2 x 50 ml), acidified to pH3 with concentrated hydrochloric acid and extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with saturated brine (2 x 50 ml), dried over anhydrous magnesium sulphate and filtered. The filtrate was evaporated under vacuum to give the title compound as a pale yellow oil (6.98 g, 100%), R<sub>f</sub> (silica) 0.89 (methylene chloride/methanol/ammonia, 80:20:1).

(c) 2-(2-Methoxyethoxymethyl)-3-[(1-phenacyloxycarbonyl)cyclopentyl]propanoic acid 1-naphthyl ester

To a stirred, ice-cold solution of the previous product 1.0 g, 2.55 mmole) in dry methylene chloride (30 ml) were added, successively, 1-hydroxybenzotriazole (0.38 g, 2.80 mmole), 1-naphthol (1.83 g, 12 mmole), N-methylmorpholine (0.33 g, 3.31 mmole) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.64 g, 3.31 mmole). After 10 minutes, the solution was concentrated to an oil which was stirred at room temperature for 18 hours and then dissolved in methylene chloride (200 ml). The latter solution was washed with water (50 ml), 2N hydrochloric acid (2 x 25 ml), saturated aqueous sodium bicarbonate solution (2 x 25 ml) and saturated brine (2 x 25 ml), then dried over anhydrous magnesium sulphate and filtered. Evaporation of the filtrate under vacuum gave an oil which was purified by chromatography on silica gel eluting with a hexane-ethyl acetate gradient. The appropriate fractions were combined and the solvent evaporated under vacuum to furnish the title diester as an oil (0.90 g, 68%), R<sub>f</sub> (silica) 0.57 (ethyl acetate/hexane, 1:1).

(d) 3-[(1-Carboxycyclopentyl)-2-(2-methoxyethoxymethyl)propanoic acid 1-naphthyl ester

Activated zinc dust (0.9 g, 13 mmole) was added to a stirred solution of the above diester, (0.9 g, 1.74 mmole) in glacial acetic acid (10 ml) at room temperature. After 18 hours, the reaction mixture was filtered and the filter pad washed with glacial acetic acid (2 x 20 ml) followed by methylene chloride (2 x 20 ml). The combined mother liquor and washings were evaporated under vacuum and the resulting oil azeotroped first with toluene (3 x 20 ml), then with methylene chloride (3 x 20 ml), and dissolved in diethyl ether (50 ml). The ether solution was washed with saturated aqueous sodium bicarbonate solution (3 x 20 ml), dried over anhydrous magnesium sulphate and filtered. Evaporation of the filtrate under vacuum provided an oil which was purified by chromatography on silica gel using a chloroform to 5% methanol in chloroform elution gradient. Evaporation of the appropriate fractions afforded the title compound as an oil (0.63 g, 91%), R<sub>f</sub> (silica) 0.18-0.36 (ethyl acetate/hexane, 1:1).

55 (e) 3-{1-[(cis-4-Benzoyloxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid 1-naphthyl ester

To a stirred, ice-cold solution of the previous product (0.77 g, 1.92 mmole) in dry methylene chloride

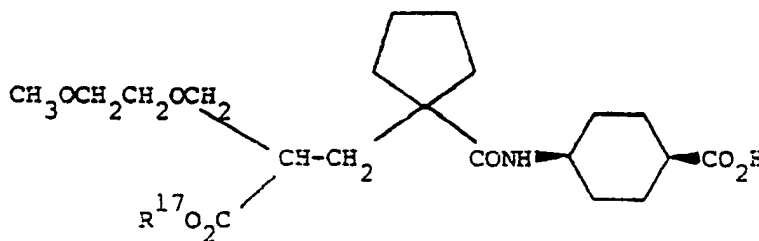
(20 ml) were added successively, 1-hydroxybenzotriazole (0.29 g, 2.11 mmole), cis-4-amino-cyclohexane-carboxylic acid benzyl ester p-toluenesulphonate (0.78 g, 1.92 mmole), N-methylmorpholine (0.45 g, 4.42 mmole) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.45 g, 2.50 mmole). After 10 minutes, the resulting solution was concentrated to an oil which was stirred at room temperature for 18 hours. The product was dissolved in ethyl acetate (200 ml) and washed with water (2 x 25 ml), 1N hydrochloric acid (2 x 25 ml), saturated aqueous sodium bicarbonate solution (2 x 25 ml) and saturated brine (2 x 25 ml), then dried over anhydrous magnesium sulphate and filtered. Evaporation of the filtrate under vacuum gave an oil which was purified by chromatography on silica gel using hexane-ethyl acetate (3:2) as eluent. The appropriate fractions were combined and the solvent evaporated under vacuum to furnish the title compound as an oil (0.94 g, 79%), R<sub>f</sub> (silica) 0.20 (ethyl acetate/hexane, 2:3), 0.77 (ethyl acetate).

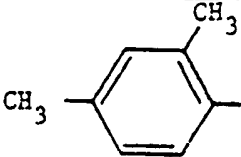
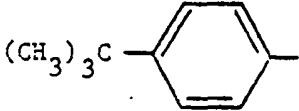
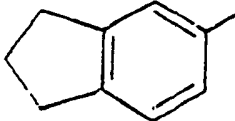
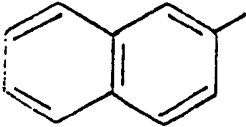
(f) 3-{1-[(cis-4-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid 1-naphthyl ester hemihydrate

A stirred solution of the previous product (0.80 g, 1.3 mmole) in 5% aqueous ethanol was hydrogenated over 10% palladium on charcoal catalyst (80 mg) at 60 p.s.i. (4.1 bar) and room temperature for 4.5 hours. The catalyst was removed by filtration and the filtrate evaporated under vacuum. The resulting group was azeotroped with methylene chloride (3 x 20 ml) to provide the title ester as a tacky white foam (0.64 g, 92%). Found: C,67.81; H,7.62; N,2.68. C<sub>30</sub>H<sub>39</sub>NO<sub>7</sub>, 0.5 H<sub>2</sub>O requires C,67.39; H,7.54; N,2.62%.

#### EXAMPLES 420-423

The following compounds were prepared following the procedure of Example 419, using the appropriate aromatic alcohol for the esterification in Step 419(c).



Example No.	R <sup>17</sup>	Analysis % (Theoretical in brackets)		
		C	H	N
420		65.50 (66.77)	8.23 8.20	2.74 2.78)
421		67.10 (67.76)	8.62 8.53	2.72 2.63)
422		67.75 (67.55)	8.07 8.02	2.67 2.72)
423		66.65 (66.82)	7.62 7.57	2.41 2.60) (1)

(1) 0.75 hydrate

40 **EXAMPLE 424**3-{1-[(cis-4-{5-Indanyloxycarbonyl}cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxy)propanoic acid(a) Preparation of cis-4-benzoyloxycarbonylaminocyclohexane carboxylic acid

45 Sodium carbonate (4.03 g, 38 mmole) was added in small portions to a stirred solution of cis-4-aminocyclohexane carboxylic acid (10.0 g, 69 mmole) in a mixture of dioxane (80 ml) and water (40 ml). After 15 minutes a solution of dibenzyl dicarbonate (19.47 g, 68 mmole) in dioxane (40 ml) was added dropwise followed by water (40 ml). The mixture was stirred for 18 hours at room temperature, the solvent evaporated under vacuum and the residue partitioned between diethyl ether and water. The organic phase  
 50 was washed with dilute hydrochloric acid and water, dried over sodium sulphate and evaporated under vacuum to give cis-4-benzoyloxycarbonylaminocyclohexane carboxylic acid as an oil (14.5 g, 75%). Found: C,64.88; H,6.98; N,5.13. C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub> requires C,64.97; H,6.91; N,5.05%.

(b) cis-4-Benzoyloxycarbonylamino-cyclohexanecarboxylic acid 5-indanyl ester

55 To a stirred, ice-cold solution of the product from part (a) (1.70 g, 6.13 mmole) in dry methylene chloride (30 ml) were added sequentially, 1-hydroxybenzotriazole (0.92 g, 6.77 mmole), 5-indanol (2.0 g, 15 mmole), N-methylmorpholine (0.80 g, 7.92 mmole) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hy-

drochloride (1.53 g, 7.98 mmole). After 10 minutes, the resulting solution was concentrated to an oil which was stirred at room temperature for 18 hours and then dissolved in methylene chloride (150 ml). The latter solution was washed in turn with water (2 x 50 ml), saturated aqueous sodium bicarbonate solution (2 x 25 ml), 2N hydrochloric acid (2 x 25 ml) and saturated brine (2 x 25 ml), then dried over anhydrous magnesium sulphate and filtered. Evaporation of the solvent under vacuum, gave an oil which was purified by chromatography on silica gel eluting with hexane-ethyl acetate (4:1). The appropriate fractions were combined and the solvent evaporated under vacuum to furnish the title compound as a white solid (2.20 g, 91%), which was crystallised from a mixture of diethyl ether and n-pentane, m.p. 68-69° C. Found: C,73.30; H,7.04; N,3.43. C<sub>24</sub>H<sub>27</sub>NO<sub>4</sub> requires C,73.26; H,6.92; N,3.56%.

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(c) cis-4-Aminocyclohexanecarboxylic acid 5-indanyl ester hydrochloride 1/4 hydrate

A stirred solution of the previous product (1.10 g, 2.8 mmole) in ethanol (50 ml) and concentrated hydrochloric acid (3 ml) was hydrogenated over 10% palladium on charcoal catalyst (110 mg) at 60 p.s.i. (4.1 bar) and room temperature for 2 hours. The catalyst was removed by filtration and the filtrate evaporated under vacuum to provide the title compound as a cream solid (0.77 g, 91%), which was crystallised from hexane-tetrahydrofuran, m.p. 163-164° C. Found: C,63.86; H,7.52; N,4.70. C<sub>15</sub>H<sub>21</sub>NO<sub>2</sub>·HCl·0.25 H<sub>2</sub>O requires C,63.98; H,7.54; N,4.66%.

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(d) 2-(2-Methoxyethoxymethyl)-3-[(1-phenacyloxy carbonyl)cyclopentyl]propanoic acid benzyl ester

Anhydrous potassium carbonate (10.55 g, 0.076 mole) was added to a stirred solution of 2-(2-methoxyethoxymethyl)-3-[(1-phenacyloxy carbonyl)cyclopentyl]propanoic acid (Example 14(b), 15.0 g, 0.038 mole) and benzyl bromide (6.53 g, 0.038 m) in dry dimethylformamide (100 ml). The resulting suspension was stirred at room temperature for 18 hours, then the bulk of the solvent was removed under vacuum and the residue partitioned between ethyl acetate (150 ml) and water (100 ml). The organic phase was separated, washed successively with water (50 ml), 1N hydrochloric acid (50 ml), and saturated aqueous sodium bicarbonate solution (50 ml), then dried over anhydrous magnesium sulphate. Filtration, followed by evaporation of the solvent under vacuum afforded the title benzyl ester as an oil (16.2 g, 88%), R<sub>f</sub> (silica) 0.69 (ethyl acetate/toluene, 1:1), 0.88 (ethyl acetate).

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(e) 3-(1-Carboxycyclopentyl)-2-(2-methoxyethoxymethyl)propanoic acid benzyl ester

Activated zinc dust (5.0 g, 0.076 mole) was added to a stirred solution of the previous product (8.0 g, 0.0165 mole) in glacial acetic acid (50 ml) at room temperature. After 3 hours, the reaction mixture was filtered and the filter pad washed with glacial acetic acid. The combined mother liquor and washings were evaporated under vacuum and the oily residue first azeotroped with toluene (3 x 40 ml), then dissolved in saturated aqueous sodium bicarbonate solution (100 ml). This aqueous solution was washed with n-hexane (3 x 50 ml), acidified to pH 3-4 with 2M hydrochloric acid and extracted with diethyl ether (2 x 100 ml). The combined ether extracts were dried over anhydrous magnesium sulphate and evaporated under vacuum. The residue was azeotroped with methylene chloride (2 x 40 ml) to afford the title compound as a yellow oil (5.15 g, 84%), R<sub>f</sub> (silica) 0.25-0.50 (ethyl acetate), 0.85 (methylene chloride/methanol/ammonia, 80:20:1).

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(f) 3-{1-[(cis-4-{5-Indanyloxy carbonyl}cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid benzyl ester

45

To a stirred, ice-cold solution of the previous product (0.92 g, 2.52 mmole) in dry methylene chloride (30 ml) were added, sequentially, 1-hydroxybenzotriazole (0.38 g, 2.74 mmole), a solution of cis-4-aminocyclohexanecarboxylic acid 5-indanyl ester hydrochloride 1/4 hydrate from part (c) (0.77 g, 2.52 mmole) in dry methylene chloride (20 ml), N-methylmorpholine (0.58 g, 5.74 mmole) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.63 g, 3.25 mmole). After 10 minutes, the resulting solution was concentrated to an oil which was stirred at room temperature for 72 hours and then diluted with methylene chloride (250 ml). The latter solution was washed in turn with water (2 x 50 ml), 2N hydrochloric acid (2 x 50 ml), saturated aqueous sodium bicarbonate solution (2 x 50 ml) and saturated brine (2 x 50 ml), then dried over anhydrous magnesium sulphate and filtered. Evaporation of the solvent under vacuum, gave an oil which was purified by chromatography on silica gel eluting with a mixture of hexane and ethyl acetate (2:1). The appropriate fractions were combined and the solvent evaporated under vacuum to furnish the title diester as an oil (1.40 g, 91%), R<sub>f</sub> (silica) 0.33 (ethyl acetate/hexane, 1:1).

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(g) 3-{1-[(cis-4-{5-Indanyloxycarbonyl}cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)-propanoic acid

A stirred solution of the previous product (1.40 g, 2.3 mmole) in ethanol (50 ml) was hydrogenated over 10% palladium on charcoal catalyst (140 mg) at 60 p.s.i. (4.1 bar) and room temperature for 18 hours. The catalyst was removed by filtration and the filtrate evaporated under vacuum to give an oil which was azeotroped with methylene chloride (3 x 40 ml) to provide the title compound as an oil (0.95 g, 81%), R<sub>f</sub> (silica) 0.90 (methylene chloride/methanol/ammonia, 80:20:1). Found: C,66.25; H,7.70; N,2.72. C<sub>29</sub>H<sub>41</sub>NO<sub>7</sub>, 0.2 CH<sub>2</sub>Cl<sub>2</sub> requires C,65.84; H,7.83; N,2.63%.

EXAMPLE 425

3-{1-[(cis-4-Ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid hemihydrate

- (a) Oxalyl chloride (0.26 g, 2.1 mmole) was added to a stirred, ice-cold solution of 3-(1-carboxycyclopentyl)-2-(2-methoxyethoxymethyl)propanoic acid benzyl ester (0.50 g, 1.37 mmole) in dry methylene chloride (10 ml), followed by 1 drop of dry dimethylformamide. The resulting solution was stirred at room temperature for 3.5 hours, the solvent evaporated under vacuum, and the residue azeotroped with methylene chloride (3 x 25 ml). The neat acid chloride thus obtained was treated with an ice-cold solution of cis-4-aminocyclohexanecarboxylic acid ethyl ester hydrochloride (0.28 g, 1.37 mmole) in dry methylene chloride (5 ml) followed by the dropwise addition, with stirring, of a solution of triethylamine (0.42 g, 4.11 mmole) in dry methylene chloride (5 ml). The reaction mixture was stirred at room temperature for 18 hours, then diluted with methylene chloride (200 ml) and washed in turn with 2N hydrochloric acid (2 x 50 ml), saturated aqueous sodium bicarbonate solution (2 x 50 ml) and saturated brine (2 x 50 ml) and dried over anhydrous magnesium sulphate. The solvent was evaporated under vacuum to give an oil which was purified by chromatography on silica gel eluting with a mixture of hexane and ethyl acetate (3:2). The appropriate fractions were combined and the solvent evaporated under vacuum to afford 3-{1-[(cis-4-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid benzyl ester as an oil (0.51 g, 72%), R<sub>f</sub> (silica) 0.40 (ethyl acetate/hexane, 1:1).
- (b) A stirred solution of the product from part (a) (0.50 g, 0.965 mmole) in 5% aqueous ethanol (40 ml) was hydrogenated over 10% palladium on charcoal catalyst (50 mg) at 60 p.s.i. (4.1 bar) and room temperature for 18 hours. The catalyst was removed by filtration and the filtrate evaporated under vacuum to yield a gum which was azeotroped with methylene chloride (3 x 40 ml) and dried under high vacuum to give the desired ethyl ester as a gum (0.41 g, 100%), Found: C,60.48; H,8.79; N,3.30. C<sub>22</sub>H<sub>37</sub>NO<sub>7</sub>, 0.5 H<sub>2</sub>O requires C,60.52; H,8.77; N,3.21%.

EXAMPLE 426

3-{1-[(cis-4-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid benzyl ester

(a) cis-4-Amino-cyclohexanecarboxylic acid t-butyl ester hydrochloride

- cis-4-Benzoyloxycarbonylamino-cyclohexanecarboxylic acid (Example 19(a) (14.5 g, 52 mmole) was dissolved in dichloromethane (100 ml) and cooled to -78°C. Liquid isobutylene (100 ml), and concentrated sulphuric acid (1.0 ml) were added, and the reaction mixture sealed in a pressure bottle and allowed to warm to room temperature with shaking overnight. Excess isobutylene was vented, dilute sodium bicarbonate solution was added and the solvent removed under vacuum. The residue was partitioned between diethyl ether and dilute aqueous sodium bicarbonate and the organic phase dried over anhydrous sodium sulphate and evaporated to give an oil (35 g). Purification by column chromatography on silica gel eluting with a mixture of diethyl ether and dichloromethane followed by crystallisation from n-pentane at 0°C gave cis-4-benzoyloxycarbonylamino-cyclohexanecarboxylic acid t-butyl ester as white needles (3.77 g, 22%) m.p. 73-74°C. This product was dissolved in ethanol (200 ml) and hydrogenated at 30 p.s.i. (2.0 bar) over 10% palladium on charcoal catalyst for 4 hours at room temperature. The reaction mixture was filtered and the solvent evaporated under reduced pressure. The residue was taken up in dichloromethane, filtered and the solvent evaporated to give an oil which was dissolved in dry diethyl ether and treated with ethereal hydrogen chloride to pH 3. The resulting precipitate was collected and dried to give the title ester hydrochloride as a white solid (2.34 g, 90%) m.p. 180° (dec.). Found: C,55.95; H,9.35; N,5.68.

$C_{11}H_{21}NO_2.HCl$  requires C,56.04; H,9.41; N,5.94%.

(b) 3-{1-[(cis-4-t-Butoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid benzyl ester

The amine hydrochloride from part (a) (1.37 g, 5.76 mmole) was coupled to 3-(1-carboxycyclopentyl)-2-(2-methoxyethoxymethyl) propanoic acid benzylester (1.98 g, 5.4 mmole) from Example 434(e) following the procedure of Example 424(f) to give the title diester as an oil (2.23 g, 75%). Found: C,68.39; H,8.75; N,2.37.  $C_{31}H_{47}NO_7$  requires C,68.22; H,8.68; N,2.57%.

(c) 3-{1-[(cis-4-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid benzyl ester

The product from part (b) above (2.23 g, 4.09 mmol) was dissolved in dry trifluoroacetic acid (20 ml) and the reaction mixture stored at 0-4 °C overnight. The trifluoroacetic acid was removed under vacuum and the residue dissolved in aqueous sodium bicarbonate (50 ml) and extracted with diethyl ether (3 x 100 ml). The aqueous phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extracts were dried over anhydrous sodium sulphate and evaporated under vacuum. The residue was azeotroped with dichloromethane and dried under vacuum to give an oil which crystallised on standing to give the title benzyl ester as a white solid (1.40 g, 70%), m.p. 83-85 °C. Found: C,65.97; H,8.17; N,2.87.  $C_{27}H_{39}NO_7$  requires C,66.24; H,8.03; N,2.86%.

#### EXAMPLE 427

3-{1-[(cis-4-(2,2-Dimethylpropanoyloxymethoxycarbonyl)cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid

(a) A solution of caesium carbonate (133 mg, 0.41 mmole) in water (5 ml) was added to a solution of 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid benzyl ester (400 mg, 0.82 mmole) in acetonitrile (15 ml) and the solvent evaporated under reduced pressure. The residue was azeotroped with acetonitrile (2 x) to give the caesium salt as a foam. This was suspended in dimethylformamide (2 ml), chloromethyl pivalate (148 mg, 0.98 mmole) added and the mixture was stirred at room temperature overnight. Diethyl ether (30 ml) was added and the solution washed with water, dried over anhydrous magnesium sulphate and the solvent evaporated. The residue was chromatographed on silica eluting with a mixture of ethyl acetate and hexane (1:5) to give 3-{1-[(cis-4-(2,2-dimethylpropanoyloxymethoxycarbonyl)cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid benzyl ester as a colourless gum (510 mg, 100%). Found: C,65.45; H,8.17; N,2.49.  $C_{33}H_{49}NO_9$  requires C,65.65; H,8.18; N,2.32%.

(b) A solution of the diester from (a) above (450 mg, 0.75 mmole) in methanol (18 ml) and water (12 ml) was hydrogenated at 50 p.s.i. (3.45 bar) over 5% palladium on carbon catalyst (50 mg) at room temperature for 5 hours. The catalyst was removed by filtration and the filtrate evaporated under reduced pressure to give the desired pivaloyloxymethyl ester as a colourless gum (265 mg 69%). Found: C,60.56; H,8.50; N,2.8.  $C_{25}H_{43}NO_9$  requires C,60.80; H,8.44; N,2.73%.

#### EXAMPLE 428

3-{1-[(cis-4-{5-Indanyloxycarbonyl}cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid 5-indanyl ester

To a stirred, ice-cold solution of 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid (0.50 g, 1.25 mmole) in dry methylene chloride (30 ml) were added, sequentially, 1-hydroxybenzotriazole (0.37 g, 2.76 mmole), 5-indanol (0.67 g, 5.0 mmole), N-methylmorpholine (0.33 g, 3.3 mmole) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.62 g, 3.2 mmole). After 10 minutes, the resulting solution was concentrated to an oil which was stirred at room temperature for 18 hours. The reaction mixture was diluted with methylene chloride (120 ml) and the solution was washed in turn with water (2 x 20 ml), saturated aqueous sodium bicarbonate solution (2 x 20 ml) and saturated brine (2 x 20 ml), dried over anhydrous magnesium sulphate and filtered. Evaporation of the filtrate under vacuum gave an oil which was purified by chromatography on silica gel using a hexane-ethyl acetate elution gradient. The appropriate fractions were combined and evaporated under vacuum to afford the title bis-5-indanyl ester as an oil (0.52 g, 65%), R<sub>f</sub> (silica) 0.50 (ethyl acetate). Found: C,71.35;

H,8.01; N,2.06.  $C_{38}H_{49}NO_7$ , 0.1  $CH_2Cl_2$  requires C,71.50; H,7.74; N,2.19%.

#### EXAMPLE 429

3-{1-[(cis-3-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(3-chloropropyl)propanoic acid

3-(1-Carboxycyclopentyl)-2-(3-chloropropyl)propanoic acid t-butyl ester was prepared following the procedure of Example 38, using the propanoic ester of Example 35 and 1-chloro-3-iodopropane as starting materials. The product was isolated as an oil (71%), Rf 0.38 (silica; chloroform, hexane, 2-propanol, 2-propylamine, 200:100:20:1).

The above glutaric acid derivative was coupled with cis-3-amino-cyclohexanecarboxylic acid ethyl ester using the procedure of Example 81 to afford 3-{1-[(cis-3-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(3-chloropropyl)propanoic acid t-butyl ester as an oil (77%). Found: C,63.31; H,9.01; N,2.94.  $C_{25}H_{42}ClNO_5$  requires C,63.60; H,8.97; N,2.97%.

The above diester was treated with trifluoroacetic acid following the procedure of Example 242 to provide 3-{1-[(cis-3-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(3-chloropropyl)propanoic acid as an oil (76%). Found: C,60.13; H,8.30; N,3.10.  $C_{21}H_{34}ClNO_5$  requires C,60.63; H,8.24; N,3.37%.

The above monoester was hydrolysed using the procedure of Example 323 to furnish the title diacid as a gum (80%). Found: C,58.77; H,7.79; N,3.33.  $C_{15}H_{30}ClNO_5$  requires C,58.83; H,7.80; N,3.61%.

#### EXAMPLE 430

3-{1-[(cis-3-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-[2-(phenylsulphonyl)ethyl]propanoic acid

3-(1-Carboxycyclopentyl)-2-[2-(phenylsulphonyl)ethyl]propanoic acid t-butyl ester was prepared following the procedure of Example 38, using as starting materials the propanoic ester of Example 35 and phenyl vinyl sulphone. The product was isolated as an oil (15%). Found: C,60.25; H,7.24.  $C_{21}H_{30}O_6S$ . 0.13  $CH_2Cl_2$  requires C,60.25; H,7.24%. The above glutaric acid derivative was coupled with cis-3-amino-cyclohexanecarboxylic acid ethyl ester using the general procedure of Example 81 to yield 3-{1-[(cis-3-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-[2-(phenylsulphonyl)ethyl]propanoic acid t-butyl ester as a foam (71%). Found: C,63.53; H,8.02; N,2.38.  $C_{30}H_{45}NO_7S$  requires C,63.91; H,8.05; N,2.48%. The above diester was treated with trifluoroacetic acid using the procedure of Example 242 to give 3-{1-[(cis-3-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-[2-(phenylsulphonyl)ethyl]propanoic acid as a foam (96%). Found: C,61.90; H,7.54; N,2.86.  $C_{25}H_{37}NO_7S$  requires C,62.51; H,7.35; N,2.76%. The above monoester was hydrolysed using the general procedure of Example 323 to give the title diacid as a foam (95%). Found: C,59.00; H,6.83; N,2.51.  $C_{24}H_{33}NO_7S$ . 0.5  $H_2O$  0.1  $CH_3CO_2C_2H_5$  requires C,58.92; H,7.04; N,2.81%.

#### EXAMPLE 431

3-{1-[(cis-3-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(3-phenyl-2-propynyl)-propanoic acid

3-(1-Carboxycyclopentyl)-2-(3-phenyl-2-propynyl)-propanoic acid t-butyl ester was prepared according to the procedure of Example 38 from the propanoic ester of Example 35 and 1-bromo-3-phenyl-2-propyne. Chromatography on silica eluting with dichloromethane changing in a gradient to diethyl ether-dichloromethane (7:3) gave the product as an oil (52%). Rf (silica) 0.7 (10% methanol-dichloromethane).

The above glutarate was coupled with cis-3-aminocyclohexanecarboxylic acid ethyl ester by the procedure of Example 81 to afford 3-{1-[(cis-3-ethoxycarbonyl-cyclohexyl)carbamoyl]cyclopentyl}-2-(3-phenyl-2-propynyl)propanoic acid t-butyl ester as a foam (65%). Found: C,72.95; H,8.56; N,2.78.  $C_{31}H_{43}NO_5$  requires C,73.05; H,8.50; N,2.75%.

The above diester was treated with trifluoroacetic acid according to the procedure of Example 242 to give 3-{1-[(cis-3-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(3-phenyl-2-propynyl)propanoic acid after chromatography on silica with hexane-isopropanol (9:1), as a foam (34%). Rf (silica) 0.6 (10% methanol-dichloromethane).

The above monoester was hydrolysed according to the procedure of Example 323 to afford the title compound as a gum (91%). Found: C,69.30; H,7.57; N,3.24.  $C_{25}H_{31}NO_5$ . 0.5  $H_2O$  requires C,69.10; H,7.42; N,3.22%.

#### EXAMPLE 432

3-{1-[(cis-3-Carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-pentynyl)propanoic acid

3-(1-Carboxycyclopentyl)-2-(2-pentynyl)propanoic acid, t-butyl ester was prepared following the procedure of Example 38, using as starting materials the propanoic acid of Example 35 and 2-pentynyl bromide. The product was isolated as an oil (64%) by chromatography on silica, eluting with hexane-diethylether (1:1). The above glutaric acid derivative was coupled with cis-3-aminocyclohexanecarboxylic acid ethyl ester according to the general procedure of Example 81 to yield 3-{1-[cis-3-ethoxycarbonylcyclohexyl]-carbamoyl}cyclopentyl-2-(2-pentynyl)propanoic acid t-butyl ester as a foam (43%). Found: C,70.07; H,9.43; N,2.94.  $C_{27}H_{43}NO_5$  requires C,70.25; H,9.39; N,3.03%.

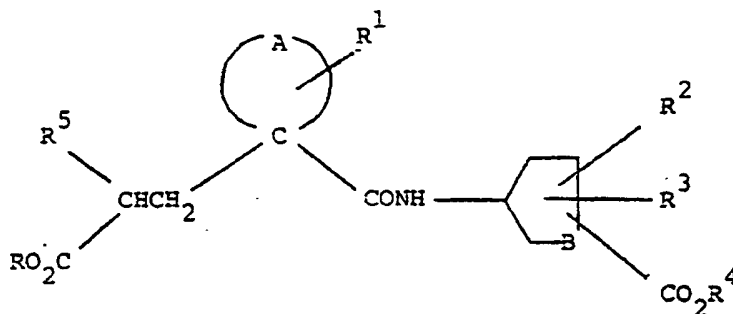
The above diester was treated with trifluoroacetic acid using the procedure of Example 242 to give 3-{1-[cis-3-ethoxycarbonylcyclohexyl]carbamoyl}cyclopentyl-2-(2-pentynyl)propanoic acid as a foam (97%). Found: C,67.76; H,8.80; N,3.36.  $C_{23}H_{35}NO_5$  requires C,68.12; H,8.70; N,3.45%.

The above monoester was hydrolysed according to the general procedure of Example 323 to give the title diacid as a foam (86%). Found: C,64.14; H,8.21; N,3.30.  $C_{21}H_{31}NO_5$ . 0.24  $CH_2Cl_2$  requires C,64.12; H,7.97; N,3.52%.

## Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound having the formula:



(I)

wherein

A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring;

B is  $(CH_2)_m$  wherein m is an integer of from 1 to 3;

each of R and R<sup>4</sup> is independently H, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl or an alternative biolabile ester-forming group;

R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> and R<sup>3</sup> are each independently H, OH, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy;

and

R<sup>5</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, aryl(C<sub>2</sub>-C<sub>6</sub> alkynyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup> or a saturated heterocyclic group;

or C<sub>1</sub>-C<sub>6</sub> alkyl substituted by one or more substituents chosen from halo, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub> hydroxyalkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy(C<sub>1</sub>-C<sub>6</sub> alkoxy), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, aryl, aryloxy, aryloxy(C<sub>1</sub>-C<sub>4</sub> alkoxy), heterocyclyl, heterocyclyloxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -SH, -S(O)<sub>p</sub>R<sup>10</sup>, -COR<sup>11</sup> or -CO<sub>2</sub>R<sup>12</sup>;

wherein

R<sup>6</sup> and R<sup>7</sup> are each independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl (optionally substituted by hydroxy or C<sub>1</sub>-C<sub>4</sub> alkoxy), aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), C<sub>2</sub>-C<sub>6</sub> alkoxy-alkyl, or heterocyclyl; or the two groups R<sup>6</sup> and R<sup>7</sup> are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C<sub>1</sub>-C<sub>4</sub> alkyl)-piperazinyl group;

R<sup>8</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

$R^9$  is  $C_1$ - $C_4$  alkyl,  $CF_3$ , aryl, aryl( $C_1$ - $C_4$  alkyl), aryl( $C_1$ - $C_4$  alkoxy), heterocyclyl,  $C_1$ - $C_4$  alkoxy or  $NR^6R^7$  wherein  $R^6$  and  $R^7$  are as previously defined;

$R^{10}$  is  $C_1$ - $C_4$  alkyl, aryl, heterocyclyl or  $NR^6R^7$  wherein  $R^6$  and  $R^7$  are as previously defined;

$R^{11}$  is  $C_1$ - $C_4$  alkyl,  $C_3$ - $C_7$  cycloalkyl, aryl or heterocyclyl;

5  $R^{12}$  is H or  $C_1$ - $C_4$  alkyl;

and

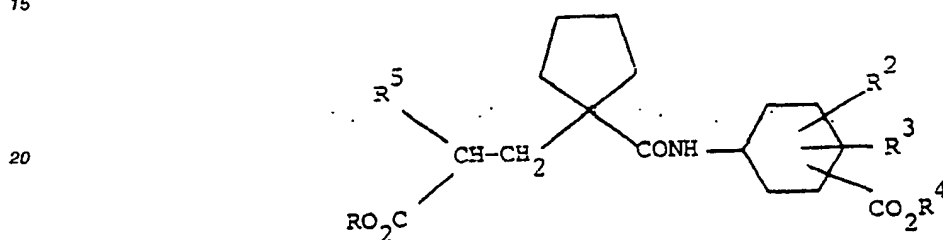
p is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof or bioprecursor therefor.

10 2. A compound as claimed in claim 1 wherein A is  $(CH_2)_n$  and n is an integer of from 3 to 6 and wherein each of R and  $R^4$  is independently H,  $C_1$ - $C_6$  alkyl or benzyl.

3. A compound as claimed in claim 1 wherein A is  $(CH_2)_4$ ,  $R^1$  is H and B is  $(CH_2)_2$  having the formula:

15



25

(II)

wherein R,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined in claim 1.

30 4. A compound as claimed in any one of claims 1 to 3 wherein R and  $R^4$  are both H.

5. A compound as claimed in claim 1 or claim 3 wherein one of R and  $R^4$  is H and the other is  $C_1$ - $C_6$  alkyl, benzyl or an alternative biolabile ester-forming group or wherein both of R and  $R^4$  are  $C_1$ - $C_6$  alkyl, benzyl or alternative biolabile ester-forming group.

35

6. A compound as claimed in claim 5 wherein one of R and  $R^4$  is H and the other is ethyl or benzyl.

7. A compound as claimed in claim 5 wherein said biolabile ester-forming group is

1-(2,2-diethylbutyryloxy)ethyl

2-ethylpropionyloxymethyl

40

1-(2-ethylpropionyloxy)ethyl

1-(2,4-dimethylbenzoyloxy)ethyl

$\alpha$ -benzoyloxybenzyl

1-(benzoyloxy)ethyl

45

2-methyl-1-propionyloxy-1-propyl

2,4,6-trimethylbenzoyloxymethyl

1-(2,4,6-trimethylbenzoyloxy)ethyl

pivaloyloxymethyl

phenethyl

phenpropyl

50

2,2,2-trifluoroethyl

1- or 2-naphthyl

2,4-dimethylphenyl

4-t-butylphenyl

55

or

5-indanyl.

8. A compound as claimed in claim 5 wherein said biolabile ester-forming group is 5-indanyl.

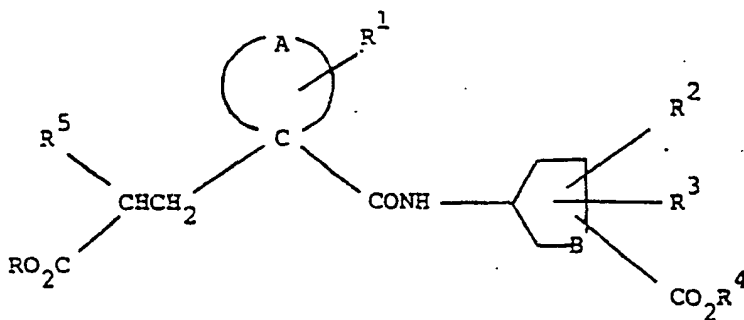
9. A compound as claimed in claim 3 wherein R, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each H and wherein the carboxy group CO<sub>2</sub>R<sup>4</sup> is attached at the 3- or 4-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group.
10. A compound as claimed in claim 3 wherein R, R<sup>2</sup> and R<sup>3</sup> are each H, R<sup>4</sup> is C<sub>2</sub>H<sub>5</sub> and wherein the ethoxycarbonyl group is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group.
11. A compound as claimed in any previous claim wherein R<sup>5</sup> is C<sub>2</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>5</sub> alkynyl, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, C<sub>5</sub>-C<sub>6</sub> cycloalkenyl, C<sub>1</sub>-C<sub>4</sub> alkylsulphonamido, or tetrahydrofuranyl or wherein R<sup>5</sup> is C<sub>1</sub>-C<sub>3</sub> alkyl substituted by C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy(C<sub>2</sub>-C<sub>4</sub> alkoxy), C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 4-pyridyl, 2-imidazolyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, C<sub>2</sub>-C<sub>4</sub> alkoxycarbonylamino, C<sub>1</sub>-C<sub>4</sub> alkylsulphonyl, C<sub>1</sub>-C<sub>4</sub> alkylsulphonamido, arylsulphonamido, heteroarylsulphonamido or benzoylamino.
12. A compound of the formula (II) as claimed in claim 3 wherein R and R<sup>4</sup> are both H, R<sup>2</sup> and R<sup>3</sup> are both H, the group CO<sub>2</sub>R<sup>4</sup> is attached at the 4-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group and wherein R<sup>5</sup> is n-propyl, methoxyethyl, 2-methoxyethoxymethyl, 2-butynyl, 2-cyclohexenyl, tetrahydrofuranyl, 4-pyridylmethyl, 2-imidazolylmethyl, acetonyl, ethylsulphonylmethyl, benzenesulphonamidomethyl, n-propylsulphonamido or 1-methoxycarbonylaminoethyl.
13. A compound of the formula (II) as claimed in claim 3 wherein R and R<sup>4</sup> are both H, R<sup>2</sup> and R<sup>3</sup> are both H, the group CO<sub>2</sub>R<sup>4</sup> is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group and wherein R<sup>5</sup> is n-propyl, 2-methoxyethoxymethyl, 2-butynyl, 2-propenyl, 2-butenyl, cyclopentyl, cyclohexyl, 2-cyclohexenyl, cyclopropylmethyl, tetrahydrofuranyl, 4-pyridylmethyl, n-propylsulphonylamino, benzenesulphonylaminomethyl or benzoylaminomethyl.
14. A compound of the formula (II) as claimed in claim 3 wherein R is H and R<sup>4</sup> is ethyl and wherein R<sup>2</sup> and R<sup>3</sup> are both H, the ethoxycarbonyl group is attached at the 3-position of the cyclohexane ring and has cis stereochemistry and R<sup>5</sup> is 2-methoxyethoxymethyl, n-propyl, 2-butynyl, 2-propenyl, cyclohexenyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, tetrahydrofuranyl, 4-pyridylmethyl, benzenesulphonamidomethyl, benzoylaminomethyl or n-propylsulphonamido.
15. A compound of the formula (I) wherein said compound is:-  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(n-propyl)propanoic acid,  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethyl)propanoic acid,  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid,  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-butynyl)propanoic acid,  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(3-tetrahydrofuranyl)propanoic acid,  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(n-propylsulphonamido)propanoic acid,  
 3-{1-[(cis-3-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(n-propyl)propanoic acid,  
 3-{1-[(cis-3-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid,  
 3-{1-[(cis-3-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-butynyl)propanoic acid,  
 3-{1-[(cis-3-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(n-propylsulphonamido)propanoic acid,  
 3-{1-[(cis-3-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid,  
 3-{1-[(cis-3-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(n-propyl)propanoic acid,  
 3-{1-[(cis-3-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(2-butynyl)propanoic acid,  
 3-{1-[(cis-3-ethoxycarbonylcyclohexyl)carbamoyl]cyclopentyl}-2-(n-propylsulphonamido)propanoic acid,  
 3-{1-[(cis-4-carboxycyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid,  
 3-{1-[(cis-4-{5-indanyloxycarbonyl}cyclohexyl)carbamoyl]cyclopentyl}-2-(2-methoxyethoxymethyl)propanoic acid.
16. A pharmaceutical composition comprising a compound of the formula (I) or (II) or a pharmaceutically acceptable salt thereof or bioprecursor therefor, as claimed in any one of claims 1 to 15, together with a pharmaceutically acceptable diluent or carrier.
17. A compound of the formula (I) (or II) as claimed in any one of claims 1 to 15 or a pharmaceutically

acceptable salt thereof or bioprecursor thereof, for use in medicine, particularly for the treatment of hypertension, heart failure or renal insufficiency.

18. A compound having the ability to inhibit the neutral endopeptidase E.C.3.4.24.11 and to thereby prevent degradation of ANF and thus potentiate its biological effects, for use in medicine, particularly for the treatment of hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menière's disease, hyperaldosteronism (primary and secondary) or hypercalciuria.
19. The use of a compound having the ability to inhibit the neutral endopeptidase E.C. 3.4.24.11 for the manufacture of a medicament to prevent degradation of ANF and thus potentiate its diuretic and natriuretic action.
20. The use of a compound having the ability to inhibit the neutral endopeptidase E.C.3.4.24.11 and to thereby prevent degradation of ANF and thus potentiate its diuretic and natriuretic action, for the manufacture of a medicament for the treatment of hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menière's disease, hyperaldosteronism (primary and secondary) or hypercalciuria.
21. The use of a compound of the formula (I) or (II) as claimed in any one of claims 1 to 15 for the manufacture of a medicament for the treatment of hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menière's disease, hyperaldosteronism (primary and secondary), hypercalciuria, glaucoma, asthma, inflammation, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhoea and irritable bowel syndrome), hyperreninaemia and the modulation of gastric acid secretion.

#### Claims for the following Contracting State : ES

1. A process for preparing a compound having the formula:



(I)

wherein

A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring;

B is (CH<sub>2</sub>)<sub>m</sub> wherein m is an integer of from 1 to 3;

each of R and R<sup>4</sup> is independently H, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl or an alternative biolabile ester-forming group;

R<sup>1</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup> and R<sup>3</sup> are each independently H, OH, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy;

and

R<sup>5</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, aryl(C<sub>2</sub>-C<sub>6</sub> alkynyl), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup> or a saturated heterocyclic group; or C<sub>1</sub>-C<sub>6</sub> alkyl substituted by one or more substituents chosen from halo, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>2</sub>-C<sub>6</sub>

hydroxyalkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy(C<sub>1</sub>-C<sub>6</sub> alkoxy), C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, aryl, aryloxy, aryloxy(C<sub>1</sub>-C<sub>4</sub> alkoxy), heterocyclyl, heterocyclyloxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -SH, -S(O)<sub>p</sub>R<sup>10</sup>, -COR<sup>11</sup> or -CO<sub>2</sub>R<sup>12</sup>;

wherein

5 R<sup>6</sup> and R<sup>7</sup> are each independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl (optionally substituted by hydroxy or C<sub>1</sub>-C<sub>4</sub> alkoxy), aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), C<sub>2</sub>-C<sub>6</sub> alkoxyalkyl, or heterocyclyl; or the two groups R<sup>6</sup> and R<sup>7</sup> are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C<sub>1</sub>-C<sub>4</sub> alkyl)-piperazinyl group;

R<sup>8</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

10 R<sup>9</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl, CF<sub>3</sub>, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), aryl(C<sub>1</sub>-C<sub>4</sub> alkoxy), heterocyclyl, C<sub>1</sub>-C<sub>4</sub> alkoxy or NR<sup>6</sup>R<sup>7</sup> wherein R<sup>6</sup> and R<sup>7</sup> are as previously defined;

R<sup>10</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl, aryl, heterocyclyl or NR<sup>6</sup>R<sup>7</sup> wherein R<sup>6</sup> and R<sup>7</sup> are as previously defined;

R<sup>11</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aryl or heterocyclyl;

R<sup>12</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

15 and

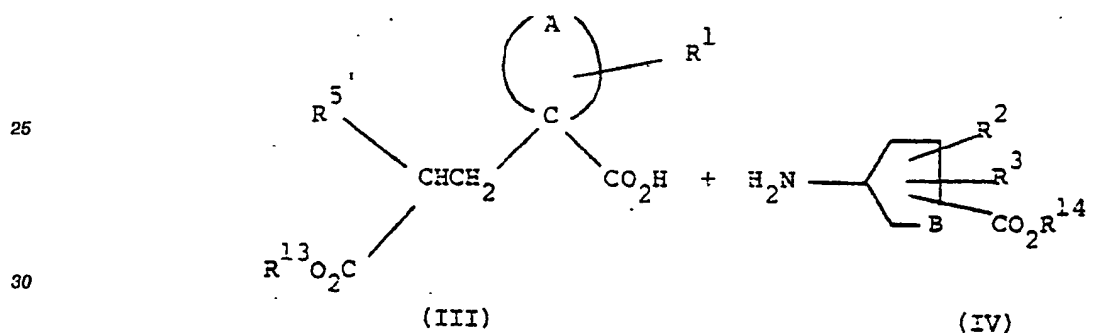
p is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof,

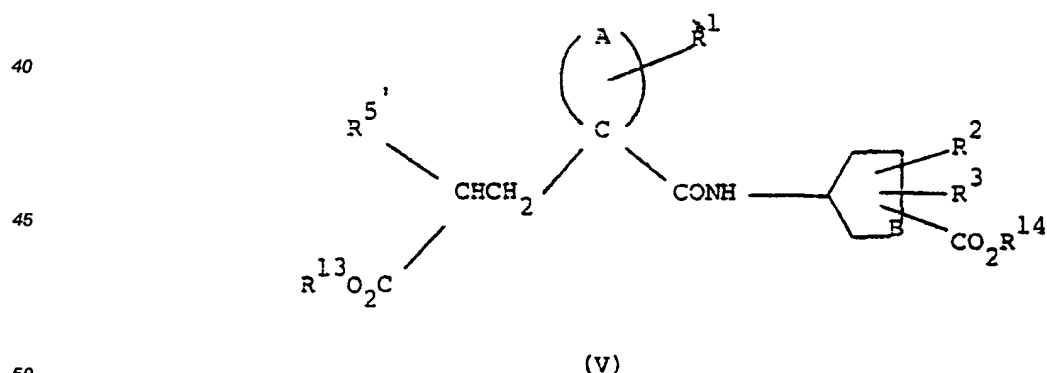
which comprises the steps of:

a) reacting compounds of the formulae:-

20



35 wherein A, B, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as previously defined, R<sup>5</sup> is as defined for R<sup>5</sup> with any reactive group therein optionally protected and R<sup>13</sup> and R<sup>14</sup> are as defined for R and R<sup>4</sup>, excluding H, or they are conventional carboxylic acid protecting groups; to produce a compound of the formula:-

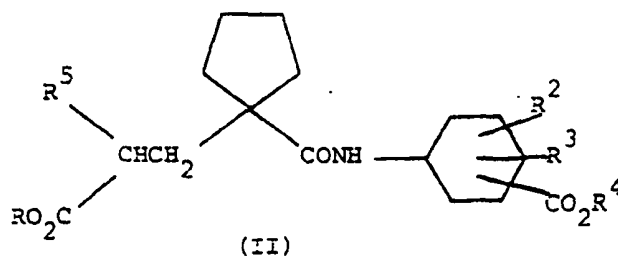


b) optionally subjecting the product to a conventional chemical transformation reaction;

55 c) in the case where one or both of R<sup>13</sup> and R<sup>14</sup> is independently C<sub>1</sub>-C<sub>6</sub> alkyl or benzyl, removing one or both of said groups; or in the case where one or both of R<sup>13</sup> and R<sup>14</sup> are conventional carboxylic acid protecting groups, removing said carboxylic acid protecting groups; and, in the case where R<sup>5</sup> contains a protecting group, removing said protecting group; to give the compound of formula (I) wherein R and R<sup>4</sup> are both H or wherein one of R and R<sup>4</sup> is H and the other is C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl or an alternative biolabile ester-forming group, and



- d) optionally esterifying the product wherein one or  $R^{13}$  and  $R^{14}$  is  $C_1$ - $C_6$  alkyl, benzyl or a conventional carboxylic acid protecting group and the other is H, with a biolabile ester-forming group followed by removal of the  $C_1$ - $C_6$  alkyl, benzyl or carboxylic acid protecting group to yield the compound of formula (I) wherein one of R and  $R^4$  is a biolabile ester-forming group and the other is H; or esterifying the product of formula (I) wherein both the R and  $R^4$  are H with a biolabile ester-forming group to yield the product of formula (I) wherein both R and  $R^4$  are biolabile ester-forming groups, and
- e) optionally forming a pharmaceutically acceptable salt of the product.
2. A process as claimed in claim 1 wherein the compounds of formulae (III) and (IV) are reacted in an organic solvent in the presence of a diimide condensing agent and said agent is 1-ethyl-3-(dimethylaminopropyl)carbodiimide or N,N'-dicyclohexylcarbodiimide.
3. A process as claimed in claim 1 wherein both of  $R^{13}$  and  $R^{14}$  are benzyl or wherein one is benzyl and the other is  $C_1$ - $C_6$  alkyl or an alternative biolabile ester-forming group, and wherein the product of formula (V) is subjected to catalytic hydrogenation to yield the compound of formula (I) wherein R and  $R^4$  are both H or wherein one is H and the other is  $C_1$ - $C_6$  alkyl or an alternative biolabile ester-forming group respectively, and wherein the product where one of R and  $R^4$  is  $C_1$ - $C_6$  alkyl is optionally hydrolysed to yield the compound of formula (I) wherein R and  $R^4$  are both H.
4. A process as claimed in claim 1 wherein one of  $R^{13}$  and  $R^{14}$  is t-butyl and the other is methyl, ethyl or benzyl, and wherein the product of formula (V) is treated with trifluoroacetic acid to yield the compound of formula (I) wherein one of R and  $R^4$  is H and the other is methyl, ethyl or benzyl, and wherein the product is optionally hydrolysed or hydrogenated to yield the compound of formula (I) wherein one of R and  $R^4$  is H and the other is methyl, ethyl or benzyl, and wherein the product is optionally hydrolysed or hydrogenated to yield the compound of formula (I) wherein R and  $R^4$  are both H.
5. A process as claimed in claim 1 wherein A is  $(CH_2)_n$  and n is an integer of from 3 to 6 and wherein each of R and  $R^4$  is independently H,  $C_1$ - $C_6$  alkyl or benzyl.
6. A process as claimed in claim 1 wherein A is  $(CH_2)_4$ ,  $R^1$  is H and B is  $(CH_2)_2$ , and the compound of formula (I) is of the formula:



wherein R,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined in claim 1.

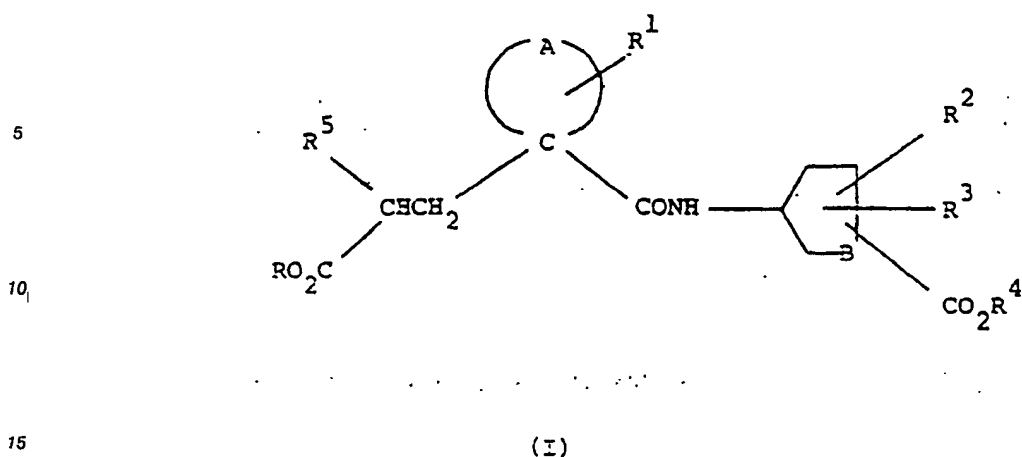
7. A process as claimed in claim 1 wherein said alternative biolabile ester-forming group is
- 1-(2,2-diethylbutyryloxy)ethyl
  - 2-ethylpropionyloxymethyl
  - 1-(2-ethylpropionyloxy)ethyl
  - 1-(2,4-dimethylbenzyloxy)ethyl
  - $\alpha$ -benzoyloxybenzyl
  - 1-(benzoyloxy)ethyl
  - 2-methyl-1-propionyloxy-1-propyl
  - 2,4,6-trimethylbenzoyloxymethyl
  - 1-(2,4,6-trimethylbenzoyloxy)ethyl
  - pivaloyloxymethyl
  - phenethyl

phenpropyl  
 2,2,2-trifluoroethyl  
 1- or 2-naphthyl  
 2,4-dimethylphenyl  
 4-t-butylphenyl  
 5-indanyl.

8. A process as claimed in claim 6 wherein R, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each H, and wherein the carboxy group CO<sub>2</sub>R<sup>4</sup> is attached at the 3- or 4-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group.
9. A process as claimed claim 6 wherein R, R<sup>2</sup> and R<sup>3</sup> are each H, R<sup>4</sup> is C<sub>2</sub>H<sub>5</sub> and wherein the ethoxycarbonyl group is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group.
10. A process as claimed in any previous claim wherein R<sup>5</sup> is C<sub>2</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>5</sub> alkynyl, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, C<sub>5</sub>-C<sub>6</sub> cycloalkenyl, C<sub>1</sub>-C<sub>4</sub> alkylsulphonamido, or tetrahydrofuranyl or wherein R<sup>5</sup> is C<sub>1</sub>-C<sub>3</sub> alkyl substituted by C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy(C<sub>2</sub>-C<sub>4</sub> alkoxy), C<sub>3</sub>-C<sub>6</sub> cycloalkyl, 4-pyridyl, 2-imidazolyl, C<sub>2</sub>-C<sub>4</sub> alkanoyl, C<sub>2</sub>-C<sub>4</sub> alkoxycarbonylamino, C<sub>1</sub>-C<sub>4</sub> alkylsulphonyl, C<sub>1</sub>-C<sub>4</sub> alkylsulphonamido, arylsulphonamido, heteroarylsulphonamido or benzoylamino.
11. A process as claimed in claim 6 wherein R and R<sup>4</sup> are both H, R<sup>2</sup> and R<sup>3</sup> are both H, the group CO<sub>2</sub>R<sup>4</sup> is attached at the 4-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group and wherein R<sup>5</sup> is n-propyl, methoxyethyl, 2-methoxyethoxymethyl, 2-butyryl, 2-cyclohexenyl, tetrahydrofuranyl, 4-pyridylmethyl, 2-imidazolylmethyl, acetonyl, ethylsulphonylmethyl, benzenesulphonamidomethyl, n-propylsulphonamido or 1-methoxycarbonylaminoethyl.
12. A process as claimed in claim 6 wherein R and R<sup>4</sup> are both H, R<sup>2</sup> and R<sup>3</sup> are both H, the group CO<sub>2</sub>R<sup>4</sup> is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group and wherein R<sup>5</sup> is n-propyl, 2-methoxyethoxymethyl, 2-butyryl, 2-propenyl, 2-butenyl, cyclopentyl, cyclohexyl, 2-cyclohexenyl, cyclopropylmethyl, tetrahydrofuranyl, 4-pyridylmethyl, n-propylsulphonylamino, benzenesulphonylaminomethyl or benzoylaminomethyl.
13. A process as claimed in claim 6 wherein R is H and R<sup>4</sup> is ethyl and wherein R<sup>2</sup> and R<sup>3</sup> are both H, the ethoxycarbonyl group is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry and R<sup>5</sup> is 2-methoxyethoxymethyl, n-propyl, 2-butyryl, 2-propenyl, cyclohexenyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, tetrahydrofuranyl, 4-pyridylmethyl, benzenesulphonamidomethyl, benzoylaminomethyl or n-propylsulphonamido.
14. A process as claimed in claim 6 wherein R<sup>2</sup> and R<sup>3</sup> are both H, the group -CO<sub>2</sub>R<sup>4</sup> is attached at the 4-position of the cyclohexane ring and has cis-stereochemistry, R<sup>5</sup> is 2-methoxyethoxymethyl and either R is 5-indanyl and R<sup>4</sup> is H or R<sup>4</sup> is 5-indanyl and R is H.

#### Claims for the following Contracting State : GR

1. A process for preparing a compound having the formula:



wherein

A completes a 4 to 7 membered carbocyclic ring which may be saturated or mono-unsaturated and which may optionally be fused to a further saturated or unsaturated 5 or 6 membered carbocyclic ring;

B is  $(CH_2)_m$  wherein m is an integer of from 1 to 3;

each of R and  $R^4$  is independently H,  $C_1$ - $C_6$  alkyl, benzyl or an alternative biolabile ester-forming group;

$R^1$  is H or  $C_1$ - $C_4$  alkyl;

$R^2$  and  $R^3$  are each independently H, OH,  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  alkoxy;

and

$R^5$  is  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl, aryl( $C_2$ - $C_6$  alkynyl),  $C_3$ - $C_7$  cycloalkyl,  $C_3$ - $C_7$  cycloalkenyl,  $C_1$ - $C_6$  alkoxy,  $-NR^6R^7$ ,  $-NR^8COR^9$ ,  $-NR^8SO_2R^9$  or a saturated heterocyclic group;

or  $C_1$ - $C_6$  alkyl substituted by one or more substituents chosen from halo, hydroxy,  $C_1$ - $C_6$  alkoxy,  $C_2$ - $C_6$  hydroxyalkoxy,  $C_1$ - $C_6$  alkoxy( $C_1$ - $C_6$  alkoxy),  $C_3$ - $C_7$  cycloalkyl,  $C_3$ - $C_7$  cycloalkenyl, aryl, aryloxy, aryloxy( $C_1$ - $C_4$  alkoxy), heterocyclyl, heterocyclyloxy,  $-NR^6R^7$ ,  $-NR^8COR^9$ ,  $-NR^8SO_2R^9$ ,  $-CONR^6R^7$ ,  $-SH$ ,  $-S(O)_pR^{10}$ ,  $-COR^{11}$  or  $-CO_2R^{12}$ ;

wherein

$R^6$  and  $R^7$  are each independently H,  $C_1$ - $C_4$  alkyl,  $C_3$ - $C_7$  cycloalkyl (optionally substituted by hydroxy or  $C_1$ - $C_4$  alkoxy), aryl, aryl( $C_1$ - $C_4$  alkyl),  $C_2$ - $C_6$  alkoxyalkyl, or heterocyclyl; or the two groups  $R^6$  and  $R^7$  are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-( $C_1$ - $C_4$  alkyl)-piperazinyl group;

$R^8$  is H or  $C_1$ - $C_4$  alkyl;

$R^9$  is  $C_1$ - $C_4$  alkyl,  $CF_3$ , aryl, aryl( $C_1$ - $C_4$  alkyl), aryl( $C_1$ - $C_4$  alkoxy), heterocyclyl,  $C_1$ - $C_4$  alkoxy or  $NR^6R^7$  wherein  $R^6$  and  $R^7$  are as previously defined;

$R^{10}$  is  $C_1$ - $C_4$  alkyl, aryl, heterocyclyl or  $NR^6R^7$  wherein  $R^6$  and  $R^7$  are as previously defined;

$R^{11}$  is  $C_1$ - $C_4$  alkyl,  $C_3$ - $C_7$  cycloalkyl, aryl or heterocyclyl;

$R^{12}$  is H or  $C_1$ - $C_4$  alkyl;

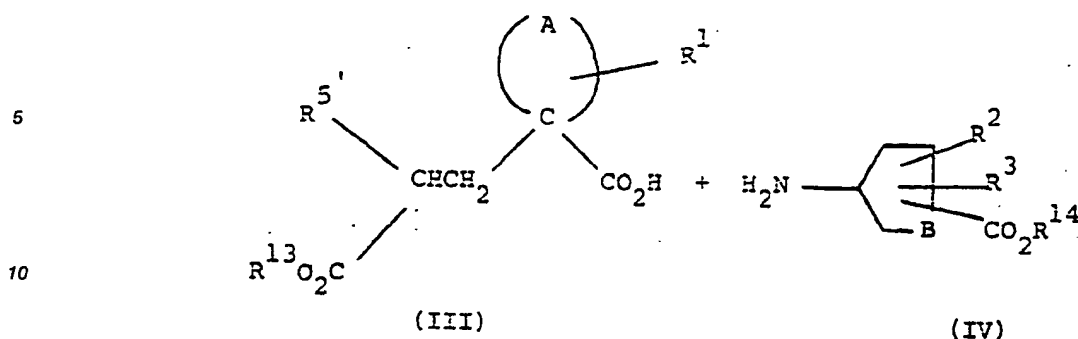
and

p is 0, or 2;

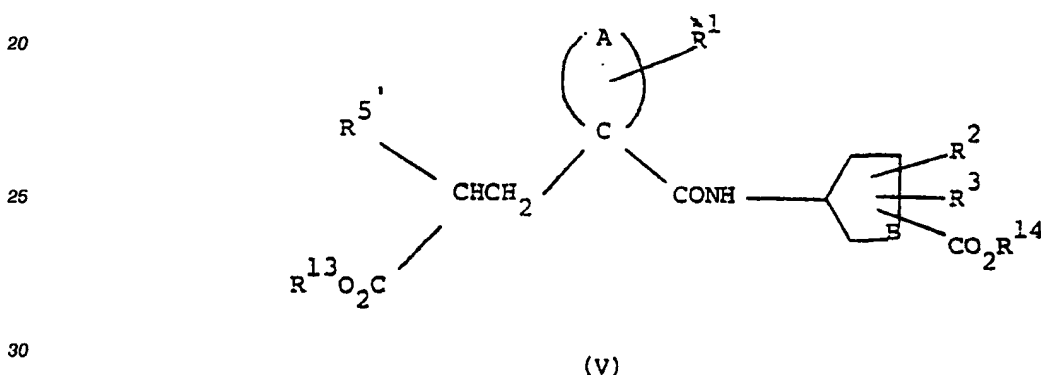
or a pharmaceutically acceptable salt thereof,

which comprises the steps of:

a) reacting compounds of the formulae:-



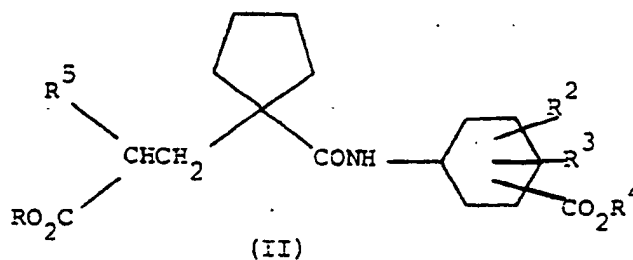
15 wherein A, B, R¹, R² and R³ are as previously defined, R⁵' is as defined for R⁵ with any reactive group therein optionally protected and R¹³ and R¹⁴ are as defined for R and R⁴, excluding H, or they are conventional carboxylic acid protecting groups; to produce a compound of the formula:-



- b) optionally subjecting the product to a conventional chemical transformation reaction;
- 35 c) in the case where one or both of R¹³ and R¹⁴ is independently C₁-C₆ alkyl or benzyl, removing one or both of said groups; or in the case where one or both of R¹³ and R¹⁴ are conventional carboxylic acid protecting groups, removing said carboxylic acid protecting groups; and, in the case where R⁵' contains a protecting group, removing said protecting group; to give the compound of formula (I) wherein R and R⁴ are both H or wherein one of R and R⁴ is H and the other is C₁-C₆ alkyl, benzyl or an alternative biolabile ester-forming group, and
- 40 d) optionally esterifying the product wherein one or R¹³ and R¹⁴ is C₁-C₆ alkyl, benzyl or a conventional carboxylic acid protecting group and the other is H, with a biolabile ester-forming group followed by removal of the C₁-C₆ alkyl, benzyl or carboxylic acid protecting group to yield the compound of formula (I) wherein one of R and R⁴ is a biolabile ester-forming group and the other is H; or esterifying the product of formula (I) wherein both the R and R⁴ are H with a biolabile ester-forming group to yield the product of formula (I) wherein both R and R⁴ are biolabile ester-forming groups, and
- 45 e) optionally forming a pharmaceutically acceptable salt of the product.

2. A process as claimed in claim 1 wherein the compounds of formulae (III) and (IV) are reacted in an organic solvent in the presence of a diimide condensing agent and said agent is 1-ethyl-3-(dimethylaminopropyl)carbodiimide or N,N'-dicyclohexylcarbodiimide.
- 50
3. A process as claimed in claim 1 wherein both of R¹³ and R¹⁴ are benzyl or wherein one is benzyl and the other is C₁-C₆ alkyl or an alternative biolabile ester-forming group, and wherein the product of formula (V) is subjected to catalytic hydrogenation to yield the compound of formula (I) wherein R and R⁴ are both H or wherein one is H and the other is C₁-C₆ alkyl or an alternative biolabile ester-forming group respectively, and wherein the product where one of R and R⁴ is C₁-C₆ alkyl is optionally hydrolysed to yield the compound of formula (I) wherein R and R⁴ are both H.
- 55

4. A process as claimed in claim 1 wherein one of  $R^{13}$  and  $R^{14}$  is t-butyl and the other is methyl, ethyl or benzyl, and wherein the product of formula (V) is treated with trifluoroacetic acid to yield the compound of formula (I) wherein one of R and  $R^4$  is H and the other is methyl, ethyl or benzyl, and wherein the product is optionally hydrolysed or hydrogenated to yield the compound of formula (I) wherein one of R and  $R^4$  is H and the other is methyl, ethyl or benzyl, and wherein the product is optionally hydrolysed or hydrogenated to yield the compound of formula (I) wherein R and  $R^4$  are both H.
5. A process as claimed in claim 1 wherein A is  $(CH_2)_n$  and n is an integer of from 3 to 6 and wherein each of R and  $R^4$  is independently H,  $C_1$ - $C_6$  alkyl or benzyl.
6. A process as claimed in claim 1 wherein A is  $(CH_2)_4$ ,  $R^1$  is H and B is  $(CH_2)_2$ , and the compound of formula (I) is of the formula:



wherein R,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined in claim 1.

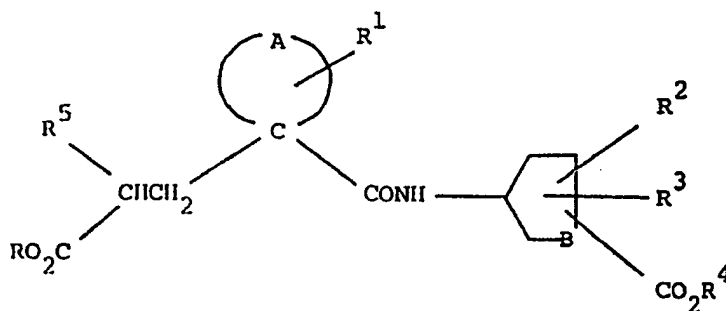
7. A process as claimed in claim 1 wherein said alternative biolabile ester-forming group is
- 1-(2,2-diethylbutyryloxy)ethyl
  - 2-ethylpropionyloxymethyl
  - 1-(2-ethylpropionyloxy)ethyl
  - 1-(2,4-dimethylbenzyloxy)ethyl
  - $\alpha$ -benzoyloxybenzyl
  - 1-(benzoyloxy)ethyl
  - 2-methyl-1-propionyloxy-1-propyl
  - 2,4,6-trimethylbenzoyloxymethyl
  - 1-(2,4,6-trimethylbenzoyloxy)ethyl
  - pivaloyloxymethyl
  - phenethyl
  - phenpropyl
  - 2,2,2-trifluoroethyl
  - 1- or 2-naphthyl
  - 2,4-dimethylphenyl
  - 4-t-butylphenyl
  - 5-indanyl.
8. A process as claimed in claim 6 wherein R,  $R^2$ ,  $R^3$  and  $R^4$  are each H, and wherein the carboxy group  $CO_2R^4$  is attached at the 3- or 4-position of the cyclohexane ring and has cis-stereo-chemistry relative to the amide group.
9. A process as claimed in claim 6 wherein R,  $R^2$  and  $R^3$  are each H,  $R^4$  is  $C_2H_5$  and wherein the ethoxycarbonyl group is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group.
10. A process as claimed in any previous claim wherein  $R^5$  is  $C_2$ - $C_4$  alkyl,  $C_2$ - $C_4$  alkenyl,  $C_2$ - $C_5$  alkynyl,  $C_5$ - $C_6$  cycloalkyl,  $C_5$ - $C_6$  cycloalkenyl,  $C_1$ - $C_4$  alkylsulphonamide, or tetrahydrofuranyl or wherein  $R^5$  is  $C_1$ - $C_3$  alkyl substituted by  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_6$  alkoxy( $C_2$ - $C_4$  alkoxy),  $C_3$ - $C_6$  cycloalkyl, 4-pyridyl, 2-imidazolyl,  $C_2$ - $C_4$  alkanoyl,  $C_2$ - $C_4$  alkoxycarbonylamino,  $C_1$ - $C_4$  alkylsulphonyl,  $C_1$ - $C_4$  alkylsulphonamido, arylsulphonamido, heteroarylsulphonamido or benzoylamino.

11. A process as claimed in claim 6 wherein R and R<sup>4</sup> are both H, R<sup>2</sup> and R<sup>3</sup> are both H, the group CO<sub>2</sub>R<sup>4</sup> is attached at the 4-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group and wherein R<sup>5</sup> is n-propyl, methoxyethyl, 2-methoxyethoxymethyl, 2-butyryl, 2-cyclohexenyl, tetrahydrofuranyl, 4-pyridylmethyl, 2-imidazolylmethyl, acetonyl, ethylsulphonylmethyl, benzenesulphonamidomethyl, n-propylsulphonamido or 1-methoxycarbonylaminoethyl.
12. A process as claimed in claim 6 wherein R and R<sup>4</sup> are both H, R<sup>2</sup> and R<sup>3</sup> are both H, the group CO<sub>2</sub>R<sup>4</sup> is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry relative to the amide group and wherein R<sup>5</sup> is n-propyl, 2-methoxyethoxymethyl, 2-butyryl, 2-propenyl, 2-butenyl, cyclopentyl, cyclohexyl, 2-cyclohexenyl, cyclopropylmethyl, tetrahydrofuranyl, 4-pyridylmethyl, n-propylsulphonylamino, benzenesulphonylamino, benzoylamino or benzoylaminoethyl.
13. A process as claimed in claim 6 wherein R is H and R<sup>4</sup> is ethyl and wherein R<sup>2</sup> and R<sup>3</sup> are both H, the ethoxycarbonyl group is attached at the 3-position of the cyclohexane ring and has cis-stereochemistry and R<sup>5</sup> is 2-methoxyethoxymethyl, n-propyl, 2-butyryl, 2-propenyl, cyclohexenyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, tetrahydrofuranyl, 4-pyridylmethyl, benzenesulphonamidomethyl, benzoylaminoethyl or n-propylsulphonamido.
14. A process as claimed in claim 6 wherein R<sup>2</sup> and R<sup>3</sup> are both H, the group -CO<sub>2</sub>R<sup>4</sup> is attached at the 4-position of the cyclohexane ring and has cis-stereochemistry, R<sup>5</sup> is 2-methoxyethoxymethyl and either R is 5-indanyl and R<sup>4</sup> is H or R<sup>4</sup> is 5-indanyl and R is H.
15. A compound of the formula (V) as defined in claim 1.

## 25 Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule :



(I)

dans laquelle

A complète un noyau carbocyclique ayant de 4 à 7 chaînons qui peut être saturé ou mono-insaturé et qui peut être éventuellement fusionné à un autre noyau carbocyclique saturé ou insaturé à 5 ou 6 chaînons ;

B est un groupe (CH<sub>2</sub>)<sub>m</sub> dans lequel m est un nombre entier compris entre 1 et 3 ;

chacun des radicaux R et R<sup>4</sup> représente, indépendamment, H, un groupe alkyle en C<sub>1</sub>-C<sub>6</sub>, benzyle ou un autre groupe formateur d'ester biolabile ;

R<sup>1</sup> représente H ou un groupe alkyle en C<sub>1</sub>-C<sub>4</sub> ;

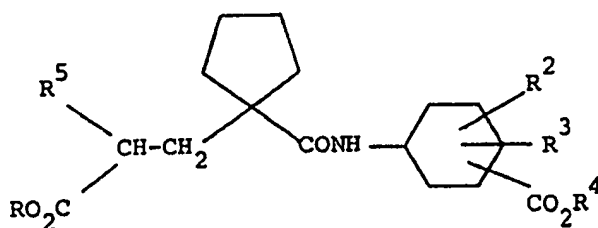
R<sup>2</sup> et R<sup>3</sup> représentent chacun, indépendamment, H, un groupe OH, alkyle en C<sub>1</sub>-C<sub>4</sub> ou alcoxy en C<sub>1</sub>-C<sub>4</sub> ;

et

R<sup>5</sup> représente un groupe alkyle en C<sub>1</sub>-C<sub>6</sub>, alkényle en C<sub>2</sub>-C<sub>6</sub>, alkynyle en C<sub>2</sub>-C<sub>6</sub>, aryl(alkynyle en C<sub>2</sub>-

- C<sub>6</sub>), cycloalkyle en C<sub>3</sub>-C<sub>7</sub>, cycloalkényle en C<sub>3</sub>-C<sub>7</sub>, alcoxy en C<sub>1</sub>-C<sub>6</sub>, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup> ou un groupe hétérocyclique saturé ;  
 ou un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> substitué par un ou plusieurs substituants choisis parmi les radicaux halogéno, hydroxy, alcoxy en C<sub>1</sub>-C<sub>6</sub>, hydroxyalcoxy en C<sub>2</sub>-C<sub>6</sub>, alcoxy en C<sub>1</sub>-C<sub>6</sub>(alcoxy en C<sub>1</sub>-C<sub>6</sub>),  
 5 cycloalkyle en C<sub>3</sub>-C<sub>7</sub>, cycloalkényle en C<sub>3</sub>-C<sub>7</sub>, aryle, aryloxy, aryloxy(alcoxy en C<sub>1</sub>-C<sub>4</sub>), hétérocyclyle, hétérocycliloxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -SH, S(O)<sub>p</sub>R<sup>10</sup> -COR<sup>11</sup> ou -CO<sub>2</sub>R<sup>12</sup> ;  
 dans lesquels  
 R<sup>6</sup> et R<sup>7</sup> représentent chacun, indépendamment, H, un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>, cycloalkyle en C<sub>3</sub>-C<sub>7</sub> -  
 (éventuellement substitué par un groupe hydroxy ou alcoxy en C<sub>1</sub>-C<sub>4</sub>), aryle, aryl(alkyle en C<sub>1</sub>-C<sub>4</sub>),  
 10 alcoxyalkyle en C<sub>2</sub>-C<sub>6</sub>, ou hétérocyclyle ; ou les deux groupes R<sup>6</sup> et R<sup>7</sup> sont pris ensemble avec l'azote auquel ils sont fixés pour former un noyau pyrrolidinyle, pipéridino, morpholino, pipérazinyle, ou N-(alkyle en C<sub>1</sub>-C<sub>4</sub>)pipérazinyle ;  
 R<sup>8</sup> représente H ou un groupe alkyle en C<sub>1</sub>-C<sub>4</sub> ;  
 R<sup>9</sup> représente un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>, CF<sub>3</sub>, aryle, aryl(alkyle en C<sub>1</sub>-C<sub>4</sub>), aryl(alcoxy en C<sub>1</sub>-C<sub>4</sub>),  
 15 hétérocyclyle, alcoxy en C<sub>1</sub>-C<sub>4</sub> ou NR<sup>6</sup>R<sup>7</sup> dans lequel R<sup>6</sup> et R<sup>7</sup> sont tels que précédemment définis ;  
 R<sup>10</sup> représente un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>, aryle, hétérocyclyle ou NR<sup>6</sup>R<sup>7</sup> dans lequel R<sup>6</sup> et R<sup>7</sup> sont tels que précédemment définis ;  
 R<sup>11</sup> représente un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>, cycloalkyle en C<sub>3</sub>-C<sub>7</sub>, aryle ou hétérocyclyle ;  
 R<sup>12</sup> représente H ou un groupe alkyle en C<sub>1</sub>-C<sub>4</sub> ;  
 20 et  
 p représente 0, 1 ou 2 ;  
 ou un sel pharmaceutiquement acceptable d'un tel composé ou d'un bioprécurseur pour un tel composé.

- 25 2. Composé selon la revendication 1, dans lequel A représente (CH<sub>2</sub>)<sub>n</sub> et n est un nombre entier compris entre 3 et 6 et dans lequel chacun des radicaux R et R<sup>4</sup> représente, indépendamment, H, un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> ou un groupe benzyle.
- 30 3. Composé selon la revendication 1, dans lequel A représente (CH<sub>2</sub>)<sub>4</sub>, R<sup>1</sup> représente H et B représente (CH<sub>2</sub>)<sub>2</sub> répondant ainsi à la formule :



(II)

- 45 dans laquelle R, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> sont tels que définis dans la revendication 1.
4. Composé selon l'une quelconque des revendications 1 à 3, dans lequel R et R<sup>4</sup> représentent tous deux H.
- 50 5. Composé selon la revendication 1 ou la revendication 3, dans lequel l'un des radicaux R et R<sup>4</sup> représente H et l'autre est un groupe alkyle en C<sub>1</sub>-C<sub>6</sub>, benzyle ou un autre groupe formateur d'ester biolabile, ou les radicaux R et R<sup>4</sup> sont tous deux des radicaux alkyle en C<sub>1</sub>-C<sub>6</sub>, benzyle ou des autres groupes formateurs d'esters biolabiles.
- 55 6. Composé selon la revendication 5, dans lequel l'un des radicaux R et R<sup>4</sup> représente H et l'autre est un groupe éthyle ou benzyle.
7. Composé selon la revendication 5, dans lequel ledit groupe formateur d'ester biolabile est un groupe

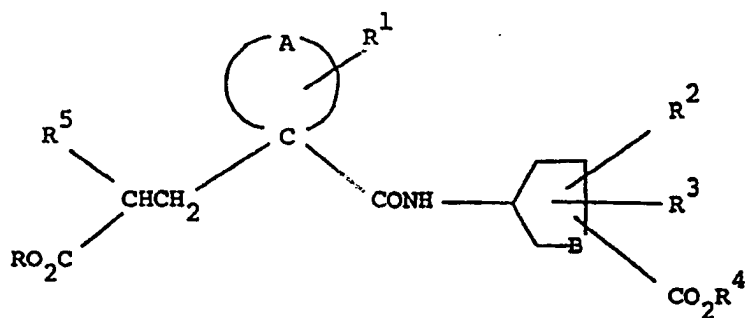
- 1-(2,2-diéthylbutyryloxy)éthyle  
 2-éthylpropionyloxyméthyle  
 1-(2-éthylpropionyloxy)éthyle  
 1-(2,4-diméthylbenzoyloxy)éthyle  
 5  $\alpha$ -benzoyloxybenzyle  
 1-(benzoyloxy)éthyle  
 2-méthyl-1-propionyloxy-1-propyle  
 2,4,6-triméthylbenzoyloxyméthyle  
 1-(2,4,6-triméthylbenzoyloxy)éthyle  
 10 pivaloyloxyméthyle  
 phénéthyle  
 phenpropyle  
 2,2,2-trifluoroéthyle  
 1- ou 2-naphtyle  
 15 2,4-diméthylphényle  
 4-t-butylphényle  
 ou  
 5-indanyle.
- 20 8. Composé selon la revendication 5, dans lequel ledit groupe formateur d'ester biolabile est le groupe 5-indanyle.
9. Composé selon la revendication 3, dans lequel R, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> représentent chacun H et dans lequel le groupe carboxy CO<sub>2</sub>R<sup>4</sup> est fixé en position-3 ou 4 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide.
- 25 10. Composé selon la revendication 3, dans lequel R, R<sup>2</sup> et R<sup>3</sup> représentent chacun H, R<sup>4</sup> représente C<sub>2</sub>H<sub>5</sub> et dans lequel le groupe éthoxycarbonyl est fixé en position-3 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide.
- 30 11. Composé selon l'une quelconque des revendications précédentes dans lequel R<sup>5</sup> représente un groupe alkyle en C<sub>2</sub>-C<sub>4</sub>, alkényle en C<sub>2</sub>-C<sub>4</sub>, alkynyle en C<sub>2</sub>-C<sub>5</sub>, cycloalkyle en C<sub>5</sub>-C<sub>6</sub>, cycloalkényle en C<sub>5</sub>-C<sub>6</sub>, alkylsulfonamido en C<sub>1</sub>-C<sub>4</sub>, ou tétrahydrofuranyle ou dans lequel R<sup>5</sup> représente un groupe alkyle en C<sub>1</sub>-C<sub>3</sub> substitué par un groupe alcoxy en C<sub>1</sub>-C<sub>3</sub> alcoxy en C<sub>1</sub>-C<sub>5</sub> (alcoxy en C<sub>2</sub>-C<sub>4</sub>), cycloalkyle en C<sub>3</sub>-C<sub>5</sub>, 4-pyridyle, 2-imidazolyle, alcanoyl en C<sub>2</sub>-C<sub>4</sub>, (alcoxy en C<sub>2</sub>-C<sub>4</sub>)carbonylamino, (alkyle en C<sub>1</sub>-C<sub>4</sub>)-sulfonyl, (alkyle en C<sub>1</sub>-C<sub>4</sub>)sulfonamido, arylsulfonamido, hétéroarylsulfonamido ou benzoylamino.
- 35 12. Composé de formule (II) selon la revendication 3, dans lequel R et R<sup>4</sup> représentent tous deux H, R<sup>2</sup> et R<sup>3</sup> représentent tous deux H, le groupe CO<sub>2</sub>R<sup>4</sup> est fixé en position-4 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide et dans lequel R<sup>5</sup> est un groupe n-propyle, méthoxyéthyle, 2-méthoxyéthoxyméthyle, 2-butynyle, 2-cyclohexényle, tétrahydrofuranyle, 4-pyridylméthyle, 2-imidazolylméthyle, acétonyl, éthylsulfonylméthyle, benzènesulfonamidométhyle, n-propylsulfonamido ou 1-méthoxycarbonylaminoéthyle.
- 40 13. Composé de formule (II) selon la revendication 3, dans lequel R et R<sup>4</sup> représentent tous deux H, R<sup>2</sup> et R<sup>3</sup> représentent tous deux H, le groupe CO<sub>2</sub>R<sup>4</sup> est fixé en position-3 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide et dans lequel R<sup>5</sup> est un groupe n-propyle, 2-méthoxyéthoxyméthyle, 2-butynyle, 2-propényle, 2-butényle, cyclopentyle, cyclohexyle, 2-cyclohexényle, cyclopropylméthyle, tétrahydrofuranyle, 4-pyridylméthyle, 2-propylsulfonylamino, benzènesulfonylaminométhyle ou benzoylaminométhyle.
- 45 50 14. Composé de formule (II) selon la revendication 3, dans lequel R représente H, et R<sup>4</sup> représente un groupe éthyle et dans lequel R<sup>2</sup> et R<sup>3</sup> représentent tous deux H, le groupe éthoxycarbonyl est fixé en position-3 sur le noyau cyclohexane et a une stéréochimie cis et R<sup>5</sup> est un groupe 2-méthoxyéthoxyméthyle, n-propyle, 2-butynyle, 2-propényle, cyclohexényle, cyclohexyle, cyclopentyle, cyclopropylméthyle, tétrahydrofuranyle, 4-pyridylméthyle, benzènesulfonamidométhyle, benzoylaminométhyle ou n-propylsulfonamido.
- 55



15. Composé de formule (I) qui est :
- l'acide 3-{1-((cis-4-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(n-propyl)propanoïque,  
 l'acide 3-{1-((cis-4-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(2-méthoxyéthyl)propanoïque,  
 l'acide 3-{1-((cis-4-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(2-méthoxyéthoxyméthyl)-  
 5 propanoïque,  
 l'acide 3-{1-((cis-4-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(2-butynyl)propanoïque,  
 l'acide 3-{1-((cis-4-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(3-tétrahydrofuranyl)propanoïque,  
 l'acide 3-{1-((cis-4-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(n-propylsulfonamido)propanoïque,  
 l'acide 3-{1-((cis-3-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(n-propyl)propanoïque,  
 10 l'acide 3-{1-((cis-3-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(2-méthoxyéthoxyméthyl)-  
 propanoïque,  
 l'acide 3-{1-((cis-3-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(2-butynyl)propanoïque,  
 l'acide 3-{1-((cis-3-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(n-propylsulfonamido)propanoïque,  
 l'acide 3-{1-((cis-3-éthoxycarbonylcyclohexyl)carbamoyl)cyclopentyl}-2-(2-méthoxyéthoxyméthyl)-  
 15 propanoïque,  
 l'acide 3-{1-((cis-3-éthoxycarbonylcyclohexyl)carbamoyl)cyclopentyl}-2-(n-propyl)propanoïque,  
 l'acide 3-{1-((cis-3-éthoxycarbonylcyclohexyl)carbamoyl)cyclopentyl}-2-(2-butynyl)propanoïque,  
 l'acide 3-{1-((cis-3-éthoxycarbonylcyclohexyl)carbamoyl)cyclopentyl}-2-(n-propylsulfonamido)-  
 propanoïque,  
 20 l'estér de 5-indanyle de l'acide 3-{1-((cis-4-carboxycyclohexyl)carbamoyl)cyclopentyl}-2-(2-méthoxyéthoxyméthyl)-propanoïque, ou  
 l'acide 3-{1-((cis-4-{5-indanyloxy-carbonyl}cyclohexyl)carbamoyl)cyclopentyl}-2-(2-méthoxyéthoxyméthyl)propanoïque.
- 25 16. Composition pharmaceutique comprenant un composé de formule (I) ou (II) ou un sel pharmaceutiquement acceptable d'un tel composé, ou un bioprécurseur d'un tel composé, selon l'une quelconque des revendications 1 à 15, avec un diluant ou un véhicule pharmaceutiquement acceptable.
- 30 17. Composé de formule (I) ou (II) selon l'une quelconque des revendications 1 à 15, ou un sel pharmaceutiquement acceptable d'un tel composé, ou un bioprécurseur pour un tel composé, destiné à l'utilisation en médecine en particulier pour le traitement de l'hypertension, des défaillances cardiaques ou de l'insuffisance rénale.
- 35 18. Composé ayant la capacité d'inhiber l'endopeptidase neutre E.C.3.4.24.11 et ainsi d'empêcher la dégradation du FNA et, donc, de potentialiser ses effets biologiques destinés à l'utilisation en médecine, en particulier pour le traitement de l'hypertension, des défaillances cardiaques, de l'angine de poitrine, de l'insuffisance rénale, du syndrome prémenstruel, de l'oedème cyclique, de la maladie de Ménière, de l'hyperaldostéronisme (primaire et secondaire) et de l'hypercalciurie.
- 40 19. Utilisation d'un composé ayant la capacité d'inhiber l'endopeptidase neutre E.C.3.4.24.11 pour la fabrication d'un médicament adapté à prévenir la dégradation du FNA et, donc, à potentialiser son action diurétique et natriurétique.
- 45 20. Utilisation d'un composé ayant la capacité d'inhiber l'endopeptidase neutre E.C.3.4.24.11 et ainsi à prévenir la dégradation du FNA et, donc, à potentialiser son action diurétique et natriurétique pour la fabrication d'un médicament de traitement de l'hypertension, des défaillances cardiaques, de l'angine de poitrine, de l'insuffisance rénale, du syndrome prémenstruel, de l'oedème cyclique, de la maladie de Ménière, de l'hyperaldostéronisme (primaire et secondaire) et de l'hypercalciurie.
- 50 21. Utilisation d'un composé de formule (I) ou (II) selon l'une quelconque des revendications 1 à 15, pour la fabrication d'un médicament pour le traitement de l'hypertension, des défaillances cardiaques, de l'angine de poitrine, de l'insuffisance rénale, du syndrome prémenstruel, de l'oedème cyclique, de la maladie de Ménière, de l'hyperaldostéronisme (primaire et secondaire), de l'hypercalciurie, du glaucome, de l'asthme, de l'inflammation, de la douleur, de l'épilepsie, des désordres affectifs, de la démence, de la confusion gériatrique, de l'obésité, des désordres gastro-intestinaux (en particulier de la diarrhée et du syndrome d'intestin irritable), de l'hyperhémoglobémie et de la modulation de la sécrétion de l'acide gastrique.
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## Rev ndications pour l'Etat contractant suivant : ES

## 1. Procédé de préparation d'un composé de formule :



(I)

dans laquelle

A complète un noyau carbocyclique ayant de 4 à 7 chaînons qui peut être saturé ou mono-insaturé et qui peut être éventuellement fusionné à un autre noyau carbocyclique saturé ou insaturé à 5 ou 6 chaînons ;

B est un groupe  $(CH_2)_m$  dans lequel  $m$  est un nombre entier compris entre 1 et 3 ;

chacun des radicaux  $R$  et  $R^4$  représente, indépendamment, H, un groupe alkyle en  $C_1-C_6$ , benzyle ou un autre groupe formateur d'ester biolabile ;

$R^1$  représente H ou un groupe alkyle en  $C_1-C_4$  ;

$R^2$  et  $R^3$  représentent chacun, indépendamment, H, un groupe OH, alkyle en  $C_1-C_4$  ou alcoxy en  $C_1-C_4$  ;

et

$R^5$  représente un groupe alkyle en  $C_1-C_6$ , alkényle en  $C_2-C_6$ , alkynyle en  $C_2-C_6$ , aryl(alkynyle en  $C_2-C_6$ ), cycloalkyle en  $C_3-C_7$ , cycloalkényle en  $C_3-C_7$ , alcoxy en  $C_1-C_6$ ,  $-NR^6R^7$ ,  $-NR^8COR^9$ ,  $-NR^8SO_2R^9$  ou un groupe hétérocyclique saturé ;

ou un groupe alkyle en  $C_1-C_6$  substitué par un ou plusieurs substituants choisis parmi les radicaux halogéno, hydroxy, alcoxy en  $C_1-C_6$ , hydroxyalcoxy en  $C_2-C_6$ , alcoxy en  $C_1-C_6$  (alcoxy en  $C_1-C_6$ ), cycloalkyle en  $C_3-C_7$ , cycloalkényle en  $C_3-C_7$ , aryle, aryloxy, aryloxy(alcoxy en  $C_1-C_4$ ), hétérocyclyle, hétérocyclioxy,  $-NR^6R^7$ ,  $-NR^8COR^9$ ,  $-NR^8SO_2R^9$ ,  $-CONR^6R^7$ ,  $-SH$ ,  $-5(O)_pR^{10}$ ,  $-COR^{11}$  ou  $CO_2R^{12}$  ;

dans lesquels

$R^6$  et  $R^7$  représentent chacun, indépendamment, H, un groupe alkyle en  $C_1-C_4$ , cycloalkyle en  $C_3-C_7$  - (éventuellement substitué par un groupe hydroxy ou alcoxy en  $C_1-C_4$ ), aryle, aryl(alkyle en  $C_1-C_4$ ), alcoxyalkyle en  $C_2-C_6$ , ou hétérocyclyle ; ou les deux groupes  $R^6$  et  $R^7$  sont pris ensemble avec l'azote auquel ils sont fixés pour former un noyau pyrrolidinyne, pipéridino, morpholino, pipérazinyne, ou N-(alkyle en  $C_1-C_4$ )pipérazinyne ;

$R^8$  représente H ou un groupe alkyle en  $C_1-C_4$  ;

$R^9$  représente un groupe alkyle en  $C_1-C_4$ ,  $CF_3$ , aryle, aryl(alkyle en  $C_1-C_4$ ), aryl(alcoxy en  $C_1-C_4$ ), hétérocyclyle, alcoxy en  $C_1-C_4$  ou  $NR^6R^7$  dans lequel  $R^6$  et  $R^7$  sont tels que précédemment définis ;

$R^{10}$  représente un groupe alkyle en  $C_1-C_4$ , aryle, hétérocyclyle ou  $NR^6R^7$  dans lequel  $R^6$  et  $R^7$  sont tels que précédemment définis ;

$R^{11}$  représente un groupe alkyle en  $C_1-C_4$ , cycloalkyle en  $C_3-C_7$ , aryle ou hétérocyclyle ;

$R^{12}$  représente H ou un groupe alkyle en  $C_1-C_4$  ;

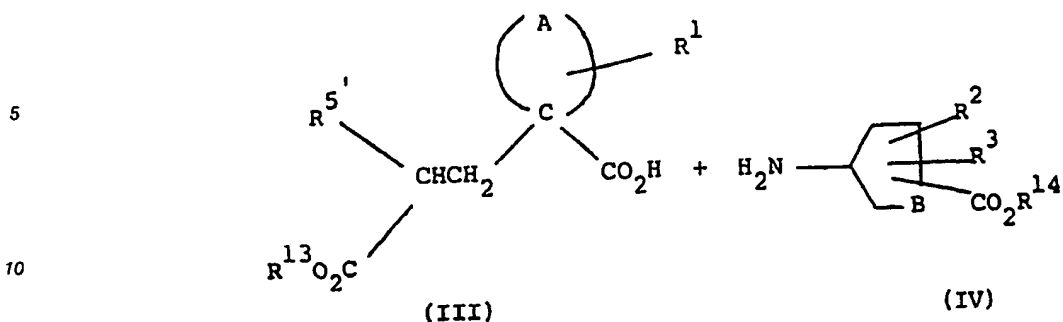
et

$p$  représente 0, 1 ou 2 ;

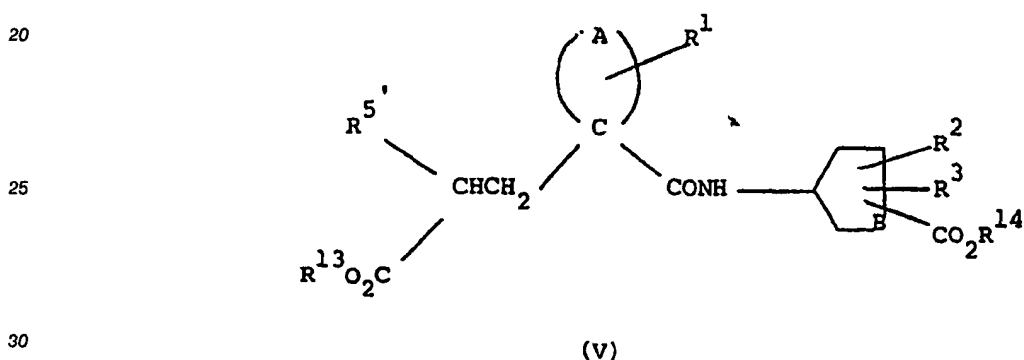
ou un sel pharmaceutiquement acceptable d'un tel composé,

qui consiste :

a) à faire réagir des composés de formule :



15 dans laquelle A, B, R<sup>1</sup>, R<sup>2</sup> et R<sup>3</sup> sont tels que précédemment définis, R<sup>5'</sup> est tel que défini pour R<sup>5</sup> avec une protection de tout groupe réactif éventuellement présent, et R<sup>13</sup> et R<sup>14</sup> sont tels que définis pour R et R<sup>4</sup>, à l'exclusion de H, ou ils représentent des groupes protecteurs classiques de la fonction acide carboxylique ; pour produire un composé de formule :



- b) à éventuellement soumettre le produit à une réaction de transformation chimique classique ;
- c) dans le cas où l'un des radicaux R<sup>13</sup> et R<sup>14</sup>, ou les deux, représentent indépendamment un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> ou benzyle, à éliminer ce ou ces dits groupes ; ou dans le cas où l'un des radicaux R<sup>13</sup> et R<sup>14</sup>, ou les deux, sont des groupes protecteurs classiques de la fonction acide carboxylique, à éliminer lesdits groupes protecteurs de la fonction acide carboxylique ; et, dans le cas où R<sup>5'</sup> comporte un groupe protecteur, à enlever ledit groupe protecteur ; pour donner le composé de formule (I) dans laquelle R et R<sup>4</sup> représentent tous deux H ou dans laquelle l'un des radicaux R et R<sup>4</sup> représente H et l'autre est un radical alkyle en C<sub>1</sub>-C<sub>6</sub>, benzyle ou un autre groupe formateur d'ester biolabile, et
- d) éventuellement à estérifier le produit dans lequel l'un des radicaux R<sup>13</sup> et R<sup>14</sup> est un groupe alkyle en C<sub>1</sub>-C<sub>6</sub>, benzyle ou un groupe protecteur classique de la fonction acide carboxylique et l'autre représente H, avec un groupe formateur d'ester biolabile suivi de l'élimination du radical alkyle en C<sub>1</sub>-C<sub>6</sub>, benzyle ou du groupe protecteur de la fonction acide carboxylique pour donner le composé de formule (I) dans laquelle l'un des radicaux R et R<sup>4</sup> est un groupe formateur d'ester biolabile et l'autre représente H ; ou à estérifier le produit de formule (I) dans laquelle les deux radicaux R et R<sup>4</sup> représentent H avec un groupe formateur d'ester biolabile pour donner le composé de formule (I) dans lequel les deux radicaux R et R<sup>4</sup> sont des groupesformateurs d'esters biolabiles, et
- e) éventuellement à former un sel pharmaceutiquement acceptable du produit.

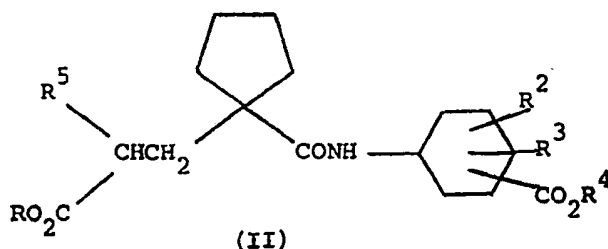
2. Procédé selon la revendication 1, dans lequel on fait réagir les composés de formules (III) et (IV) dans un solvant organique en présence d'un agent de condensation diimide et en ce que ledit agent est le 1-éthyl-3-(diméthylaminopropyl)carbodiimide ou le N,N'-dicyclohexylcarbodiimide.
3. Procédé selon la revendication 1, dans lequel tant R<sup>13</sup> que R<sup>14</sup> sont des groupes benzyle ou dans lequel l'un est un groupe benzyle et l'autre un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> ou un autre groupe formateur

d'estér biolabile, et dans lequel le produit de formule (v) est soumis à une hydrogénation catalytique pour donner le composé de formule (I) dans laquelle R et R<sup>4</sup> représentent tous deux H ou dans laquelle, respectivement, l'un représente H et l'autre représente un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> ou un autre groupe formateur d'estér biolabile et où le produit dans lequel l'un des radicaux R et R<sup>4</sup> représente un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> est éventuellement hydrolysé pour donner le composé de formule (I) dans laquelle R et R<sup>4</sup> représentent tous deux H.

4. Procédé selon la revendication 1, dans lequel l'un des radicaux R<sup>13</sup> et R<sup>14</sup> représente un groupe t-butyle et l'autre un groupe méthyle, éthyle ou benzyle, et dans lequel le produit de formule (V) est traité avec de l'acide trifluoroacétique pour donner le composé de formule (I) dans laquelle l'un des radicaux R et R<sup>4</sup> représente H et l'autre représente un groupe méthyle, éthyle ou benzyle, et dans lequel le produit est éventuellement hydrolysé ou hydrogéné pour donner le composé de formule (I) dans laquelle R et R<sup>4</sup> représentent tous deux H.

5. Procédé selon la revendication 1, dans lequel A représente (CH<sub>2</sub>)<sub>n</sub> et n est un nombre entier compris entre 3 et 6 et dans lequel chacun des radicaux R et R<sup>4</sup> représente, indépendamment, H, un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> ou un groupe benzyle.

6. Procédé selon la revendication 1, dans lequel A représente (CH<sub>2</sub>)<sub>4</sub>, R<sup>1</sup> représente H et B représente (CH<sub>2</sub>)<sub>2</sub> répondant ainsi à la formule :



dans laquelle R, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et R<sup>5</sup> sont tels que définis dans la revendication 1.

7. Procédé selon la revendication 1, dans lequel ledit groupe formateur d'estér biolabile est un groupe

1-(2,2-diéthylbutyryloxy)éthyle  
 2-éthylpropionyloxyméthyle  
 1-(2-éthylpropionyloxy)éthyle  
 1-(2,4-diméthylbenzoyloxy)éthyle  
 α-benzoyloxybensyle  
 1-(benzoyloxy)éthyle  
 2-méthyl-1-propionyloxy-1-propyle  
 2,4,6-triméthylbenzoyloxyméthyle  
 1-(2,4,6-triméthylbenzoyloxy)éthyle  
 pivaloyloxyméthyle  
 phénéthyle  
 phenpropyle  
 2,2,2-trifluoroéthyle  
 1- ou 2-naphtyle  
 2,4-diméthylphényle  
 4-t-butylphényle

ou

5-indanyle.

8. Procédé selon la revendication 6, dans lequel R, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> représentent chacun H et dans lequel le groupe carboxy CO<sub>2</sub>R<sup>4</sup> est fixé en position-3 ou 4 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide.

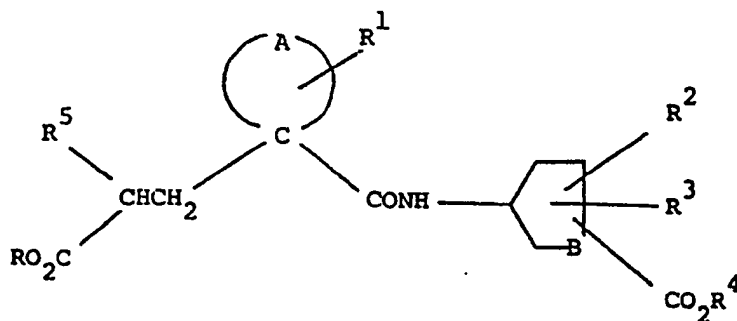
9. Procédé selon la revendication 6, dans lequel R, R<sup>2</sup> et R<sup>3</sup> représentent chacun H, R<sup>4</sup> représente C<sub>2</sub>H<sub>5</sub>

et dans lequel le groupe éthoxycarbonyl est fixé en position-3 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide.

10. Procédé selon l'une quelconque des revendications précédentes, dans lequel  $R^5$  représente un groupe alkyle en  $C_2-C_4$ , alkényle en  $C_2-C_4$ , alkynyle en  $C_2-C_5$ , cycloalkyle en  $C_5-C_6$ , cycloalkényle en  $C_5-C_6$ , alkylsulfonamido en  $C_1-C_4$ , ou tétrahydrofuranyl ou dans lequel  $R^5$  représente un groupe alkyle en  $C_1-C_3$  substitué par un groupe alcoxy en  $C_1-C_3$ , alcoxy en  $C_1-C_6$  (alcoxy en  $C_2-C_4$ ), cycloalkyle en  $C_3-C_6$ , 4-pyridyle, 2-imidazolyle, alcanoyl en  $C_2-C_4$ , (alcoxy en  $C_2-C_4$ )carbonylamino, (alkyle en  $C_1-C_4$ )-sulfonyl, (alkyle en  $C_1-C_4$ )sulfonamido, arylsulfonamido, hétéroarylsulfonamido ou benzoylamino.
11. Procédé selon la revendication 6, dans lequel R et  $R^4$  représentent tous deux H,  $R^2$  et  $R^3$  représentent tous deux H, le groupe  $CO_2R^4$  est fixé en position-4 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide et dans lequel  $R^5$  est un groupe n-propyle, méthoxyéthyle, 2-méthoxyéthoxyméthyle, 2-butynyle, 2-cyclohexényle, tétrahydrofuranyl, 4-pyridylméthyle, 2-imidazolylméthyle, acétonyle, éthylsulfonylméthyle, benzènesulfonamidométhyle, n-propylsulfonamido ou 1-méthoxycarbonylaminoéthyle.
12. Procédé selon la revendication 6, dans lequel R et  $R^4$  représentent tous deux H,  $R^2$  et  $R^3$  représentent tous deux H, le groupe  $CO_2R^4$  est fixé en position-3 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide et dans lequel  $R^5$  est un groupe n-propyle, 2-méthoxyéthoxyméthyle, 2-butynyle, 2-propényle, 2-butényle, cyclopentyle, cyclohexyle, 2-cyclohexényle, cyclopropylméthyle, tétrahydrofuranyl, 4-pyridylméthyle, n-propylsulfonylamino, benzènesulfonylaminométhyle ou benzoylaminométhyle.
13. Procédé selon la revendication 6, dans lequel R représente H, et  $R^4$  représente un groupe éthyle et dans lequel  $R^2$  et  $R^3$  représentent tous deux H, le groupe éthoxycarbonyl est fixé en position-3 sur le noyau cyclohexane et a une stéréochimie cis et  $R^5$  est un groupe 2-méthoxyéthoxyméthyle, n-propyle, 2-butynyle, 2-propényle, cyclohexényle, cyclohexyle, cyclopentyle, cyclopropylméthyle, tétrahydrofuranyl, 4-pyridylméthyle, benzènesulfonamidométhyle, benzoylaminométhyle ou n-propylsulfonamido.
14. Procédé selon la revendication 6, dans lequel  $R^2$  et  $R^3$  représentent tous deux H, le groupe  $-CO_2R^4$  est fixé en position 4 sur le noyau cyclohexane et il a une stéréochimie cis,  $R^5$  est un groupe 2-méthoxyéthoxyméthyle et soit R est un groupe 5-indanyl et  $R^4$  représente H, soit  $R^4$  est un groupe 5-indanyl et R représente H.

#### Revendications pour l'Etat contractant suivant : GR

1. Procédé de préparation d'un composé de formule :



(I)

dans laquelle

A complète un noyau carbocyclique ayant de 4 à 7 chaînons qui peut être saturé ou mono-insaturé et

qui peut être éventuellement fusionné à un autre noyau carbocyclique saturé ou insaturé à 5 ou 6 chaînons ;

B est un groupe  $(CH_2)_m$  dans lequel m est un nombre entier compris entre 1 et 3 ;

chacun des radicaux R et R<sup>4</sup> représente, indépendamment, H, un groupe alkyle en C<sub>1</sub>-C<sub>6</sub>, benzyle ou un autre groupe formateur d'ester biolabile ;

R<sup>1</sup> représente H ou un groupe alkyle en C<sub>1</sub>-C<sub>4</sub> ;

R<sup>2</sup> et R<sup>3</sup> représentent chacun, indépendamment, H, un groupe OH, alkyle en C<sub>1</sub>-C<sub>4</sub> ou alcoxy en C<sub>1</sub>-C<sub>4</sub> ;

et

R<sup>5</sup> représente un groupe alkyle en C<sub>1</sub>-C<sub>6</sub>, alkényle en C<sub>2</sub>-C<sub>6</sub>, alkynyle en C<sub>2</sub>-C<sub>6</sub>, aryl(alkynyle en C<sub>2</sub>-C<sub>6</sub>), cycloalkyle en C<sub>3</sub>-C<sub>7</sub>, cycloalkényle en C<sub>3</sub>-C<sub>7</sub>, alcoxy en C<sub>1</sub>-C<sub>6</sub>, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup> ou un groupe hétérocyclique saturé ;

ou un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> substitué par un ou plusieurs substituants choisis parmi les radicaux halogéno, hydroxy, alcoxy en C<sub>1</sub>-C<sub>6</sub>, hydroxyalcoxy en C<sub>2</sub>-C<sub>6</sub>, alcoxy en C<sub>1</sub>-C<sub>6</sub>(alcoxy en C<sub>1</sub>-C<sub>6</sub>), cycloalkyle en C<sub>3</sub>-C<sub>7</sub>, cycloalkényle en C<sub>3</sub>-C<sub>7</sub>, aryle, aryloxy, aryloxy(alcoxy en C<sub>1</sub>-C<sub>4</sub>), hétérocyclyle, hétérocycliloxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -SH, -S(O)<sub>p</sub>R<sup>10</sup>, -COR<sup>11</sup> ou -CO<sub>2</sub>R<sup>12</sup> ; dans lesquels

R<sup>6</sup> et R<sup>7</sup> représentent chacun, indépendamment, H, un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>, cycloalkyle en C<sub>3</sub>-C<sub>7</sub> - (éventuellement substitué par un groupe hydroxy ou alcoxy en C<sub>1</sub>-C<sub>4</sub>), aryle, aryl(alkyle en C<sub>1</sub>-C<sub>4</sub>), alcoxyalkyle en C<sub>2</sub>-C<sub>6</sub>, ou hétérocyclyle ; ou les deux groupes R<sup>6</sup> et R<sup>7</sup> sont pris ensemble avec l'azote auquel ils sont fixés pour former un noyau pyrrolidine, pipéridino, morpholino, pipérazinyle, ou N-(alkyle en C<sub>1</sub>-C<sub>4</sub>)pipérazinyle ;

R<sup>8</sup> représente H ou un groupe alkyle en C<sub>1</sub>-C<sub>4</sub> ;

R<sup>9</sup> représente un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>, CF<sub>3</sub>, aryle, aryle(alkyle en C<sub>1</sub>-C<sub>4</sub>), aryl(alcoxy en C<sub>1</sub>-C<sub>4</sub>), hétéroaryl(alkyle en C<sub>1</sub>-C<sub>4</sub>), aryl(alcoxy en C<sub>1</sub>-C<sub>4</sub>), hétérocyclyle, alcoxy en C<sub>1</sub>-C<sub>4</sub> ou NR<sup>6</sup>R<sup>7</sup> dans lequel R<sup>6</sup> et R<sup>7</sup> sont tels que précédemment définis ;

R<sup>10</sup> représente un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>, aryle, hétérocyclyle ou NR<sup>6</sup>R<sup>7</sup> dans lequel R<sup>6</sup> et R<sup>7</sup> sont tels que précédemment définis ;

R<sup>11</sup> représente un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>, cycloalkyle en C<sub>3</sub>-C<sub>7</sub>, aryle ou hétérocyclyle ;

R<sup>12</sup> représente H ou un groupe alkyle en C<sub>1</sub>-C<sub>4</sub> ;

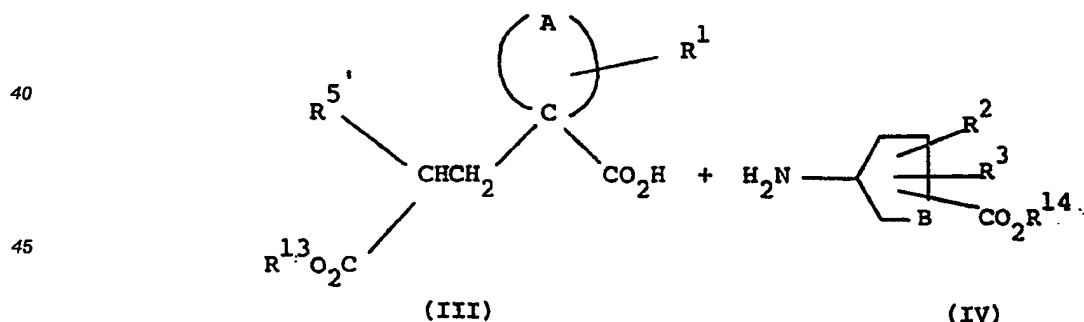
et

p représente 0, 1 ou 2 ;

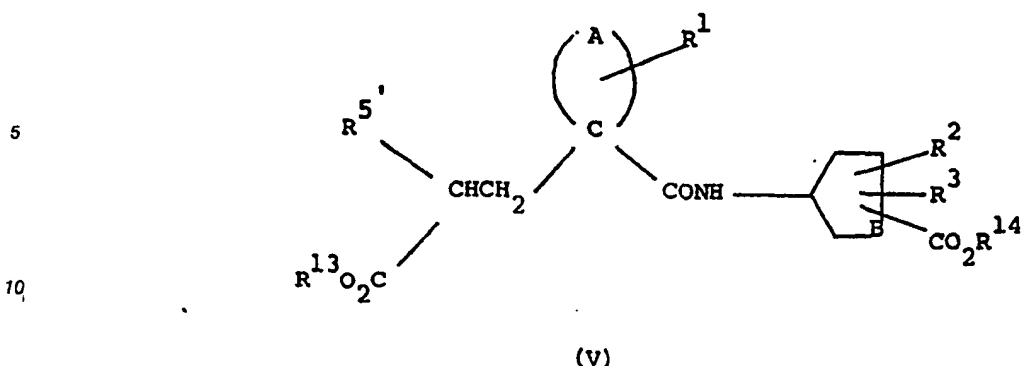
ou un sel pharmaceutiquement acceptable d'un tel composé,

qui consiste :

a) à faire réagir des composés de formule :

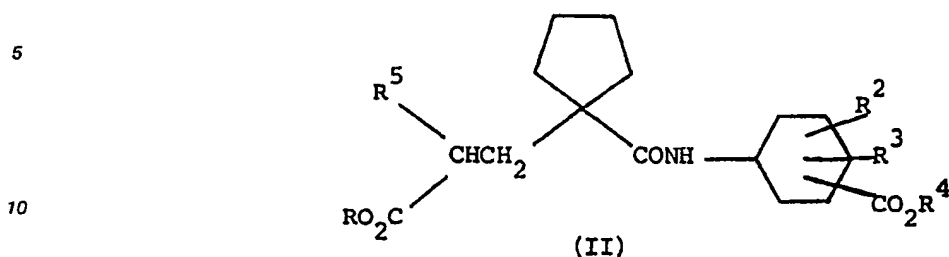


dans laquelle A, B, R<sup>1</sup>, R<sup>2</sup> et R<sup>3</sup> sont tels que précédemment définis, R<sup>5</sup> est tel que défini pour R<sup>5</sup> avec une protection de tout groupe réactif éventuellement présent, et R<sup>13</sup> et R<sup>14</sup> sont tels que définis pour R et R<sup>4</sup>, à l'exclusion de H, ou ils représentent des groupes protecteurs classiques de la fonction acide carboxylique ; pour produire un composé de formule :



- 15 b) à éventuellement soumettre le produit à une réaction de transformation chimique classique ;  
 c) dans le cas où l'un des radicaux  $R^{13}$  et  $R^{14}$ , ou les deux, représentent indépendamment un  
 groupe alkyle en  $C_1-C_6$  ou benzyle, à éliminer ce ou ces dits groupes ; ou dans le cas où l'un des  
 radicaux  $R^{13}$  et  $R^{14}$ , ou les deux, sont des groupes protecteurs classiques de la fonction acide  
 20 carboxylique, à éliminer lesdits groupes protecteurs de la fonction acide carboxylique ; et, dans le  
 cas où  $R^5$  comporte un groupe protecteur, à enlever ledit groupe protecteur ; pour donner le  
 composé de formule (I) dans laquelle R et  $R^4$  représentent tous deux H ou dans laquelle l'un des  
 radicaux R et  $R^4$  représente H et l'autre est un radical alkyle en  $C_1-C_6$ , benzyle ou un autre groupe  
 formateur d'ester biolabile, et  
 d) éventuellement à estérifier le produit dans lequel l'un des radicaux  $R^{13}$  et  $R^{14}$  est un groupe  
 25 alkyle en  $C_1-C_6$ , benzyle ou un groupe protecteur classique de la fonction acide carboxylique et  
 l'autre représente H, avec un groupe formateur d'ester biolabile suivi de l'élimination du radical  
 alkyle en  $C_1-C_6$ , benzyle ou du groupe protecteur de la fonction acide carboxylique pour donner le  
 composé de formule (I) dans laquelle l'un des radicaux R et  $R^4$  est un groupe formateur d'ester  
 biolabile et l'autre représente H ; ou à estérifier le produit de formule (I) dans laquelle les deux  
 30 radicaux R et  $R^4$  représentent H avec un groupe formateur d'ester biolabile pour donner le composé  
 de formule (I) dans lequel les deux radicaux R et  $R^4$  sont des groupes formateurs d'esters biolabiles,  
 et  
 e) éventuellement à former un sel pharmaceutiquement acceptable du produit.
- 35 2. Procédé selon la revendication 1, dans lequel on fait réagir les composés de formules (III) et (IV) dans  
 un solvant organique en présence d'un agent de condensation diimide et en ce que ledit agent est le 1-  
 éthyl-3-(diméthylaminopropyl)carbodiimide ou le N,N'-dicyclohexylcarbodiimide.
- 40 3. Procédé selon la revendication 1, dans lequel tant  $R^{13}$  que  $R^{14}$  sont des groupes benzyle ou dans  
 lequel l'un est un groupe benzyle et l'autre un groupe alkyle en  $C_1-C_6$  ou un autre groupe formateur  
 d'ester biolabile, et dans lequel le produit de formule (V) est soumis à une hydrogénation catalytique  
 pour donner le composé de formule (I) dans laquelle R et  $R^4$  représentent tous deux H ou dans  
 laquelle, respectivement, l'un représente H et l'autre représente un groupe alkyle en  $C_1-C_6$  ou un autre  
 45 groupe formateur d'ester biolabile, et où le produit dans lequel l'un des radicaux R et  $R^4$  représente un  
 groupe alkyle en  $C_1-C_6$  est éventuellement hydrolysé pour donner le composé de formule (I) dans  
 laquelle R et  $R^4$  représentent tous deux H.
- 50 4. Procédé selon la revendication 1, dans lequel l'un des radicaux  $R^{13}$  et  $R^{14}$  représente un groupe t-  
 butyle et l'autre un groupe méthyle, éthyle ou benzyle, et dans lequel le produit de formule (V) est  
 traité avec de l'acide trifluoroacétique pour donner le composé de formule (I) dans laquelle l'un des  
 radicaux R et  $R^4$  représente H et l'autre représente un groupe méthyle, éthyle ou benzyle, et dans  
 lequel le produit est éventuellement hydrolysé ou hydrogéné pour donner le composé de formule (I)  
 dans laquelle R et  $R^4$  représentent tous deux H.
- 55 5. Procédé selon la revendication 1, dans lequel A représente  $(CH_2)_n$  et n est un nombre entier compris  
 entre 3 et 6 et dans lequel chacun des radicaux R et  $R^4$  représente, indépendamment, H, un groupe  
 alkyle en  $C_1-C_6$  ou un groupe benzyle.

6. Procédé selon la revendication 1, dans lequel A représente  $(CH_2)_4$ ,  $R^1$  représente H et B représente  $(CH_2)_2$  répendant ainsi à la formule :



dans laquelle R,  $R^2$ ,  $R^3$ ,  $R^4$  et  $R^5$  sont tels que définis dans la revendication 1.

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7. Procédé selon la revendication 1, dans lequel ledit groupe formateur d'ester biolabile est un groupe
- 1-(2,2-diéthylbutyryloxy)éthyle
  - 2-éthylpropionyloxyméthyle
  - 1-(2-éthylpropionyloxy)éthyle
  - 20 1-(2,4-diméthylbenzoyloxy)éthyle
  - $\alpha$ -benzoyloxybenzyle
  - 1-(benzoyloxy)éthyle
  - 2-méthyl-1-propionyloxy-1-propyle
  - 2,4,6-triméthylbenzoyloxyméthyle
  - 25 1-(2,4,6-triméthylbenzoyloxy)éthyle
  - pivaloyloxyméthyle
  - phénéthyle
  - phenpropyle
  - 2,2,2-trifluoroéthyle
  - 30 1- ou 2-naphtyle
  - 2,4-diméthylphényle
  - 4-t-butylphényle
- ou
- 5-indanyle.
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8. Procédé selon la revendication 6, dans lequel R,  $R^2$ ,  $R^3$  et  $R^4$  représentent chacun H et dans lequel le groupe carboxy  $CO_2R^4$  est fixé en position-3 ou 4 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide.
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9. Procédé selon la revendication 6, dans lequel R,  $R^2$  et  $R^3$  représentent chacun H,  $R^4$  représente  $C_2H_5$  et dans lequel le groupe éthoxycarbonyl est fixé en position-3 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide.
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10. Procédé selon l'une quelconque des revendications précédentes, dans lequel  $R^5$  représente un groupe alkyle en  $C_2-C_4$ , alkenyle en  $C_2-C_4$ , alkynyle en  $C_2-C_5$ , cycloalkyle en  $C_5-C_6$ , cycloalkényle en  $C_5-C_6$ , alkylsulfonamido en  $C_1-C_4$ , ou tétrahydrofuranyl ou dans lequel  $R^5$  représente un groupe alkyle en  $C_1-C_3$  substitué par un groupe alcoxy en  $C_1-C_3$ , alcoxy en  $C_1-C_6$  (alcoxy en  $C_2-C_4$ ), cycloalkyle en  $C_3-C_6$ , 4-pyridyle, 2-imidazolyle, alcanoyl en  $C_2-C_4$ , (alcoxy en  $C_2-C_4$ )carbonylamino, (alkyle en  $C_1-C_4$ )sulfonyl, (alkyle en  $C_1-C_4$ )sulfonamido, arylsulfonamido, hétéroarylsulfonamido ou benzoylamino.
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11. Procédé selon la revendication 6, dans lequel R et  $R^4$  représentent tous deux H,  $R^2$  et  $R^3$  représentent tous deux H, le groupe  $CO_2R^4$  est fixé en position-4 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide et dans lequel  $R^5$  est un groupe n-propyle, méthoxyéthyle, 2-méthoxyéthoxyméthyle, 2-butynyle, 2-cyclohexényle, tétrahydrofuranyl, 4-pyridylméthyle, 2-imidazolylméthyle, acétonyl, éthylsulfonylméthyle, benzènesulfonamidométhyle, n-propylsulfonamido ou 1-méthoxycarbonylaminoéthyle.
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12. Procédé selon la revendication 6, dans lequel R et  $R^4$  représentent tous deux H,  $R^2$  et  $R^3$  représentent



tous deux H, le groupe  $\text{CO}_2\text{R}^4$  est fixé en position-3 sur le noyau cyclohexane et a une stéréochimie cis par rapport au groupe amide et dans lequel  $\text{R}^5$  est un groupe n-propyle, 2-méthoxy-éthoxyméthyle, 2-butynyle, 2-propényle, 2-butényle, cyclopentyle, cyclohexyle, 2-cyclohexényle, cyclopropylméthyle, tétrahydrofuranyle, 4-pyridylméthyle, n-propylsulfonylamino, benzènesulfonylamino ou benzoylaminométhyle.

13. Procédé selon la revendication 6, dans lequel R représente H, et  $\text{R}^4$  représente un groupe éthyle et dans lequel  $\text{R}^2$  et  $\text{R}^3$  représentent tous deux H, le groupe éthoxycarbonyl est fixé en position-3 sur le noyau cyclohexane et a une stéréochimie cis et  $\text{R}^5$  est un groupe 2-méthoxyéthoxyméthyle, n-propyle, 2-butynyle, 2-propényle, cyclohexényle, cyclohexyle, cyclopentyle, cyclopropylméthyle, tétrahydrofuranyle, 4-pyridylméthyle, benzènesulfonamidométhyle, benzoylaminométhyle ou n-propylsulfon amido.
14. Procédé selon la revendication 6, dans lequel  $\text{R}^2$  et  $\text{R}^3$  représentent tous deux H, le groupe  $-\text{CO}_2\text{R}^4$  est fixé en position 4 sur le noyau cyclohexane et il a une stéréochimie cis,  $\text{R}^5$  est un groupe 2-méthoxyéthoxyméthyle et soit R est un groupe 5-indanyle et  $\text{R}^4$  représente H, soit  $\text{R}^4$  est un groupe 5-indanyle et R représente H.
15. Composé de formule (V) tel que défini dans la revendication 1.

## 20 Patentansprüche

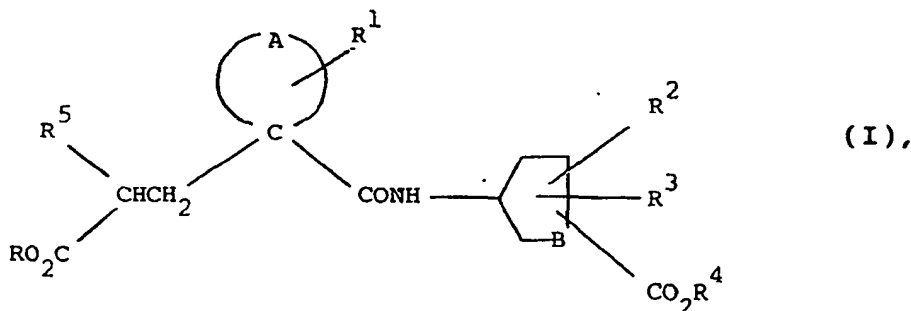
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

### 1. Verbindung der Formel

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worin A einen 4- bis 7-gliedrigen carbocyclischen Ring vervollständigt, der gesättigt oder monoungesättigt sein kann und der gegebenenfalls an einen weiteren gesättigten oder ungesättigten 5- oder 6-gliedrigen carbocyclischen Ring kondensiert sein kann;

B  $(\text{CH}_2)_m$  darstellt, wobei m eine ganze Zahl von 1 bis 3 ist;

jedes von R und  $\text{R}^4$  unabhängig H,  $\text{C}_1$ - $\text{C}_6$ -Alkyl, Benzyl oder eine alternative biolabile esterbildende Gruppe bedeutet;

$\text{R}^1$  H oder  $\text{C}_1$ - $\text{C}_4$ -Alkyl ist;

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$\text{R}^2$  und  $\text{R}^3$  unabhängig jeweils H, OH,  $\text{C}_1$ - $\text{C}_4$ -Alkyl oder  $\text{C}_1$ - $\text{C}_4$ -Alkoxy bedeuten; und

$\text{R}^5$   $\text{C}_1$ - $\text{C}_6$ -Alkyl,  $\text{C}_2$ - $\text{C}_6$ -Alkenyl,  $\text{C}_2$ - $\text{C}_6$ -Alkynyl, Aryl-( $\text{C}_2$ - $\text{C}_6$ -alkynyl),  $\text{C}_3$ - $\text{C}_7$ -Cycloalkyl,  $\text{C}_3$ - $\text{C}_7$ -Cycloalkenyl,  $\text{C}_1$ - $\text{C}_6$ -Alkoxy,  $-\text{NR}^6\text{R}^7$ ,  $-\text{NR}^8\text{COR}^9$ ,  $-\text{NR}^8\text{SO}_2\text{R}^9$  oder eine gesättigte heterocyclische Gruppe darstellt oder  $\text{C}_1$ - $\text{C}_6$ -Alkyl substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy,  $\text{C}_1$ - $\text{C}_6$ -Alkoxy,  $\text{C}_2$ - $\text{C}_6$ -Hydroxyalkoxy,  $\text{C}_1$ - $\text{C}_6$ -Alkoxy-( $\text{C}_1$ - $\text{C}_6$ -alkoxy),  $\text{C}_3$ - $\text{C}_7$ -Cycloalkyl,  $\text{C}_3$ - $\text{C}_7$ -Cycloalkenyl, Aryl, Aryloxy, Aryloxy-( $\text{C}_1$ - $\text{C}_4$ -alkoxy), Heterocyclyl, Heterocycliloxy,  $-\text{NR}^6\text{R}^7$ ,  $-\text{NR}^8\text{COR}^9$ ,  $-\text{NR}^8\text{SO}_2\text{R}^9$ ,  $-\text{CONR}^6\text{R}^7$ ,  $-\text{SH}$ ,  $-\text{S(O)}_p\text{R}^{10}$ ,  $-\text{COR}^{11}$  oder  $-\text{CO}_2\text{R}^{12}$  ist,

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wobei  $\text{R}^6$  und  $\text{R}^7$  unabhängig jeweils H,  $\text{C}_1$ - $\text{C}_4$ -Alkyl,  $\text{C}_3$ - $\text{C}_7$ -Cycloalkyl (gegebenenfalls substituiert durch Hydroxy oder  $\text{C}_1$ - $\text{C}_4$ -Alkoxy), Aryl, Aryl-( $\text{C}_1$ - $\text{C}_4$ -alkyl),  $\text{C}_2$ - $\text{C}_6$ -Alkoxyalkyl oder Heterocyclyl sind oder die beiden Gruppen  $\text{R}^6$  und  $\text{R}^7$  zusammen mit dem Stickstoff, an den sie gebunden sind, eine Pyrrolidinyl-, Piperidino-, Morpholino-, Piperazinyl- oder N-( $\text{C}_1$ - $\text{C}_4$ -Alkyl)-piperazinylgruppe bilden;

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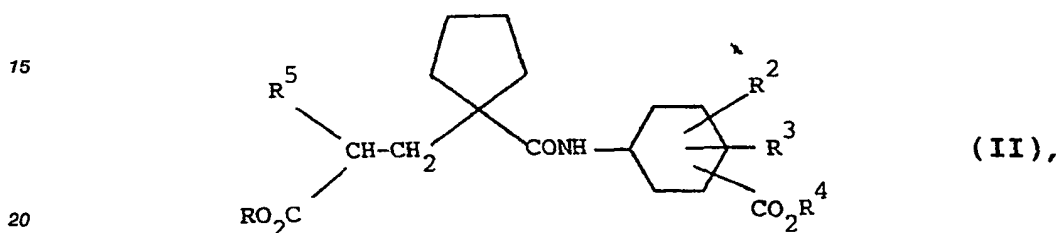
$\text{R}^8$  H oder  $\text{C}_1$ - $\text{C}_4$ -Alkyl ist;

$\text{R}^9$   $\text{C}_1$ - $\text{C}_4$ -Alkyl,  $\text{CF}_3$ , Aryl, Aryl-( $\text{C}_1$ - $\text{C}_4$ -alkyl), Aryl-( $\text{C}_1$ - $\text{C}_4$ -alkoxy), Heterocyclyl,  $\text{C}_1$ - $\text{C}_4$ -Alkoxy oder  $\text{NR}^6\text{R}^7$  darstellt, wobei  $\text{R}^6$  und  $\text{R}^7$  wie oben definiert sind;

$R^{10}$  C<sub>1</sub>-C<sub>4</sub>-Alkyl, Aryl, Heterocyclyl oder  $NR^6R^7$  bedeutet, wobei  $R^6$  und  $R^7$  wie oben definiert sind;  
 $R^{11}$  C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, Aryl oder Heterocyclyl ist;  
 $R^{12}$  H oder C<sub>1</sub>-C<sub>4</sub>-Alkyl bedeutet und  
 p Null, 1 oder 2 ist,

oder ein pharmazeutisch annehmbares Salz hiervon oder ein Biovorläufer hierfür.

2. Verbindung nach Anspruch 1, worin A die Bedeutung  $(CH_2)_n$  hat und n eine ganze Zahl von 3 bis 6 ist und worin jedes R und  $R^4$  unabhängig H, C<sub>1</sub>-C<sub>6</sub>-Alkyl oder Benzyl darstellt.
3. Verbindung nach Anspruch 1, worin A die Bedeutung  $(CH_2)_4$  hat,  $R^1$  H darstellt und B  $(CH_2)_2$  ist, der Formel



worin  $R$ ,  $R^2$ ,  $R^3$ ,  $R^4$  und  $R^5$  wie in Anspruch 1 definiert sind.

4. Verbindung nach einem der Ansprüche 1 bis 3, worin  $R$  und  $R^4$  beide H sind.
5. Verbindung nach Anspruch 1 oder 3, worin eines von  $R$  und  $R^4$  H ist und das andere C<sub>1</sub>-C<sub>6</sub>-Alkyl, Benzyl oder eine alternative biolabile esterbildende Gruppe darstellt oder worin sowohl  $R$  als auch  $R^4$  C<sub>1</sub>-C<sub>6</sub>-Alkyl, Benzyl oder alternative biolabile esterbildende Gruppen bedeuten.
6. Verbindung nach Anspruch 5, worin eines von  $R$  und  $R^4$  H bedeutet und das andere Äthyl oder Benzyl ist.
7. Verbindung nach Anspruch 5, worin die biolabile esterbildende Gruppe 1-(2,2-Diäthylbutyryloxy)-äthyl, 2-Äthylpropionyloxymethyl, 1-(2-Äthylpropionyloxy)-äthyl, 1-(2,4-Dimethylbenzoyloxy)-äthyl,  $\alpha$ -Benzoyloxybenzyl, 1-(Benzoyloxy)-äthyl, 2-Methyl-1-propionyloxy-1-propyl, 2,4,6-Trimethylbenzoyloxymethyl, 1-(2,4,6-Trimethylbenzoyloxy)-äthyl, Pivaloyloxymethyl, Phenäthyl, Phenpropyl, 2,2,2-Trifluoräthyl, 1- oder 2-Naphthyl, 2,4-Dimethyl-phenyl, 4-tert-Butylphenyl oder 5-Indanyl ist.
8. Verbindung nach Anspruch 5, worin die biolabile esterbildende Gruppe 5-Indanyl ist.
9. Verbindung nach Anspruch 3, worin  $R$ ,  $R^2$ ,  $R^3$  und  $R^4$  jeweils H sind und worin sich die Carboxygruppe  $CO_2R^4$  in Stellung 3 oder 4 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist.
10. Verbindung nach Anspruch 3, worin  $R$ ,  $R^2$  und  $R^3$  jeweils H sind,  $R^4$  die Bedeutung  $C_2H_5$  hat und worin sich die Äthoxycarbonylgruppe in Stellung 3 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist.
11. Verbindung nach einem vorhergehenden Anspruch, worin  $R^5$  C<sub>2</sub>-C<sub>4</sub>-Alkyl, C<sub>2</sub>-C<sub>4</sub>-Alkenyl, C<sub>2</sub>-C<sub>5</sub>-Alkynyl, C<sub>5</sub>-C<sub>6</sub>-Cycloalkyl, C<sub>5</sub>-C<sub>6</sub>-Cycloalkenyl, C<sub>1</sub>-C<sub>4</sub>-Alkylsulfonamido oder Tetrahydrofuranyl bedeutet oder worin  $R^5$  C<sub>1</sub>-C<sub>3</sub>-Alkyl substituiert durch C<sub>1</sub>-C<sub>3</sub>-Alkoxy, C<sub>1</sub>-C<sub>8</sub>-Alkoxy-(C<sub>2</sub>-C<sub>4</sub>-alkoxy), C<sub>3</sub>-C<sub>6</sub>-Cycloalkyl, 4-Pyridyl, 2-Imidazolyl, C<sub>2</sub>-C<sub>4</sub>-Alkanoyl, C<sub>2</sub>-C<sub>4</sub>-Alkoxycarbonylamino, C<sub>1</sub>-C<sub>4</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>4</sub>-Alkylsulfonamido, Arylsulfonamido, Heteroarylsulfonamido oder Benzoylamino darstellt.
12. Verbindung der Formel (II) nach Anspruch 3, worin  $R$  und  $R^4$  beide H bedeuten,  $R^2$  und  $R^3$  beide H darstellen, die Gruppe  $CO_2R^4$  sich in Stellung 4 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist und worin  $R^5$  n-Propyl, Methoxyäthyl, 2-Methoxyäthoxymethyl,

2-Butinyl, 2-Cyclohexenyl, Tetrahydrofuranyl, 4-Pyridylmethyl, 2-Imidazolylmethyl, Acetonyl, Äthylsulfonylmethyl, Benzolsulfonamidomethyl, n-Propylsulfonamido oder 1-Methoxycarbonylaminoäthyl bedeutet.

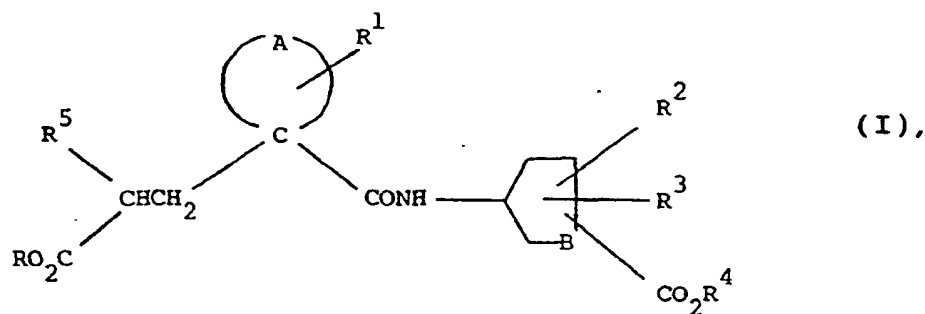
- 5 13. Verbindung der Formel (II) nach Anspruch 3, worin R und R<sup>4</sup> beide H bedeuten, R<sup>2</sup> und R<sup>3</sup> beide H darstellen, die Gruppe CO<sub>2</sub>R<sup>4</sup> sich in Stellung 3 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist und worin R<sup>5</sup> n-Propyl, 2-Methoxyäthoxymethyl, 2-Butinyl, 2-Propenyl, 2-Butenyl, Cyclopentyl, Cyclohexyl, 2-Cyclohexenyl, Cyclopropylmethyl, Tetrahydrofuranyl, 4-Pyridylmethyl, n-Propylsulfonamino, Benzolsulfonylaminomethyl oder Benzoylaminomethyl ist.
- 10 14. Verbindung der Formel (II) nach Anspruch 3, worin R H bedeutet und R<sup>4</sup> Äthyl ist und worin R<sup>2</sup> und R<sup>3</sup> beide H darstellen, die Äthoxycarbonylgruppe sich in Stellung 3 des Cyclohexanringes befindet und cis-Stereochemie aufweist und worin R<sup>5</sup> 2-Methoxyäthoxymethyl, n-Propyl, 2-Butinyl, 2-Propenyl, Cyclohexenyl, Cyclohexyl, Cyclopentyl, Cyclopropylmethyl, Tetrahydrofuranyl, 4-Pyridylmethyl, Benzolsulfonamidomethyl, Benzoylaminomethyl oder n-Propylsulfonamido ist.
- 15 15. Verbindung der Formel (I), worin die Verbindung
- 3-{1-[(cis-4-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(n-propyl)-propionsäure,  
 3-{1-[(cis-4-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(2-methoxyäthyl)-propionsäure,  
 20 3-{1-[(cis-4-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(2-methoxyäthoxymethyl)-propionsäure,  
 3-{1-[(cis-4-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(2-butinyl)-propionsäure,  
 3-{1-[(cis-4-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(3-tetrahydrofuranyl)-propionsäure,  
 3-{1-[(cis-4-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(n-propylsulfonamido)-propionsäure,  
 25 3-{1-[(cis-3-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(n-propyl)-propionsäure,  
 3-{1-[(cis-3-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(2-methoxyäthoxymethyl)-propionsäure,  
 3-{1-[(cis-3-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(2-butinyl)-propionsäure,  
 3-{1-[(cis-3-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(n-propylsulfonamido)-propionsäure,  
 3-{1-[(cis-3-Äthoxycarbonylcyclohexyl)-carbamoyl]-cyclopentyl}-2-(2-methoxyäthoxymethyl)-  
 propionsäure,  
 30 3-{1-[(cis-3-Äthoxycarbonylcyclohexyl)-carbamoyl]-cyclopentyl}-2-(n-propyl)-propionsäure,  
 3-{1-[(cis-3-Äthoxycarbonylcyclohexyl)-carbamoyl]-cyclopentyl}-2-(2-butinyl)-propionsäure,  
 3-{1-[(cis-3-Äthoxycarbonylcyclohexyl)-carbamoyl]-cyclopentyl}-2-(n-propylsulfonamido)-  
 propionsäure,  
 35 3-{1-[(cis-4-Carboxycyclohexyl)-carbamoyl]-cyclopentyl}-2-(2-methoxyäthoxymethyl)-propionsäure-  
 5-indanylester oder  
 3-{1-[(cis-4-{5-Indanyloxy-carbonyl}-cyclohexyl)-carbamoyl]-cyclopentyl}-2-(2-methoxyäthoxymethyl)-propionsäure ist.
- 40 16. Pharmazeutische Zusammensetzung umfassend eine Verbindung der Formel (I) oder (II) oder ein pharmazeutisch annehmbares Salz hievon oder einen Vorläufer hiefür, wie in einem der Ansprüche 1 bis 15 beansprucht, zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.
- 45 17. Verbindung der Formel (I) oder (II) nach einem der Ansprüche 1 bis 15 oder ein pharmazeutisch annehmbares Salz hievon oder ein Biovorläufer hiefür zur Verwendung in der Medizin, insbesondere für die Behandlung von Bluthochdruck, Herzschwäche oder Niereninsuffizienz.
- 50 18. Verbindung mit der Fähigkeit, die neutrale Endopeptidase E.C.3.4.24.11 zu inhibieren und dadurch Abbau von ANF zu verhindern und so dessen biologische Wirkungen zu verstärken, zur Verwendung in der Medizin, insbesondere für die Behandlung von Bluthochdruck, Herzschwäche, Angina, Niereninsuffizienz, prämenstruellem Syndrom, zyklischem Ödem, Menière-Krankheit, Hyperaldosteronismus (primär und sekundär) oder Hyperkalzurie.
- 55 19. Verwendung einer Verbindung mit der Fähigkeit, die neutrale Endopeptidase E.C.3.4.24.11 zu inhibieren, zur Herstellung eines Medikaments zum Verhindern von Abbau von ANF und damit zum Verstärken seiner diuretischen und natriuretischen Wirkung.
20. Verwendung einer Verbindung mit der Fähigkeit, die neutrale Endopeptidase E.C.3.4.24.11 zu inhibie-

ren und dadurch Abbau von ANF zu verhindern und damit seine diuretische und natriuretische Wirkung zu verstärken, zur Herstellung eines Medikaments für die Behandlung von Bluthochdruck, Herzschwäche, Angina, Niereninsuffizienz, prämenstruellem Syndrom, zyklischem Ödem, Menière-Krankheit, Hyperaldosteronismus (primär und sekundär) oder Hyperkalzurie.

21. Verwendung einer Verbindung der Formel (I) oder (II) nach einem der Ansprüche 1 bis 15 zur Herstellung eines Medikaments für die Behandlung von Bluthochdruck, Herzschwäche, Angina, Niereninsuffizienz, prämenstruellem Syndrom, zyklischem Ödem, Menière-Krankheit, Hyperaldosteronismus (primär und sekundär), Hyperkalzurie, Glaukom, Asthma, Entzündung, Schmerz, Epilepsie, Gemütskrankungen, Demenz und geriatrischer Verwirrung, Fettsucht und Gastrointestinalstörungen (insbesondere Diarrhoe und irritabilem Reizkolon), Hyperrenismus und Modulation der Magensäuresekretion.

#### Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zum Herstellen einer Verbindung der Formel



worin A einen 4- bis 7-gliedrigen carbocyclischen Ring vervollständigt, der gesättigt oder monoungesättigt sein kann und der gegebenenfalls an einen weiteren gesättigten oder ungesättigten 5- oder 6-gliedrigen carbocyclischen Ring kondensiert sein kann;

B  $(CH_2)_m$  darstellt, wobei m eine ganze Zahl von 1 bis 3 ist;

jedes von R und R<sup>4</sup> unabhängig H, C<sub>1</sub>-C<sub>6</sub>-Alkyl, Benzyl oder eine alternative biolabile esterbildende Gruppe bedeutet;

R<sup>1</sup> H oder C<sub>1</sub>-C<sub>4</sub>-Alkyl ist;

R<sup>2</sup> und R<sup>3</sup> unabhängig jeweils H, OH, C<sub>1</sub>-C<sub>4</sub>-Alkyl oder C<sub>1</sub>-C<sub>4</sub>-Alkoxy bedeuten; und

R<sup>5</sup> C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>2</sub>-C<sub>6</sub>-Alkenyl, C<sub>2</sub>-C<sub>6</sub>-Alkynyl, Aryl-(C<sub>2</sub>-C<sub>6</sub>-alkynyl), C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkenyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup> oder eine gesättigte heterocyclische Gruppe darstellt oder C<sub>1</sub>-C<sub>6</sub>-Alkyl substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>2</sub>-C<sub>6</sub>-Hydroxyalkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkoxy-(C<sub>1</sub>-C<sub>6</sub>-alkoxy), C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkenyl, Aryl, Aryloxy, Aryloxy-(C<sub>1</sub>-C<sub>4</sub>-alkoxy), Heterocyclyl, Heterocyclylloxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -SH, -S(O)<sub>p</sub>R<sup>10</sup>, -COR<sup>11</sup> oder -CO<sub>2</sub>R<sup>12</sup> ist,

wobei R<sup>6</sup> und R<sup>7</sup> unabhängig jeweils H, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl (gegebenenfalls substituiert durch Hydroxy oder C<sub>1</sub>-C<sub>4</sub>-Alkoxy), Aryl, Aryl-(C<sub>1</sub>-C<sub>4</sub>-alkyl), C<sub>2</sub>-C<sub>6</sub>-Alkoxyalkyl oder Heterocyclyl sind oder die beiden Gruppen R<sup>6</sup> und R<sup>7</sup> zusammen mit dem Stickstoff, an den sie gebunden sind, eine Pyrrolidiny-, Piperidino-, Morpholino-, Piperaziny- oder N-(C<sub>1</sub>-C<sub>4</sub>-Alkyl)-piperazinygruppe bilden;

R<sup>8</sup> H oder C<sub>1</sub>-C<sub>4</sub>-Alkyl ist;

R<sup>9</sup> C<sub>1</sub>-C<sub>4</sub>-Alkyl, CF<sub>3</sub>, Aryl, Aryl-(C<sub>1</sub>-C<sub>4</sub>-alkyl), Aryl-(C<sub>1</sub>-C<sub>4</sub>-alkoxy), Heterocyclyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy oder -NR<sup>6</sup>R<sup>7</sup> darstellt, wobei R<sup>6</sup> und R<sup>7</sup> wie oben definiert sind;

R<sup>10</sup> C<sub>1</sub>-C<sub>4</sub>-Alkyl, Aryl, Heterocyclyl oder -NR<sup>6</sup>R<sup>7</sup> bedeutet, wobei R<sup>6</sup> und R<sup>7</sup> wie oben definiert sind;

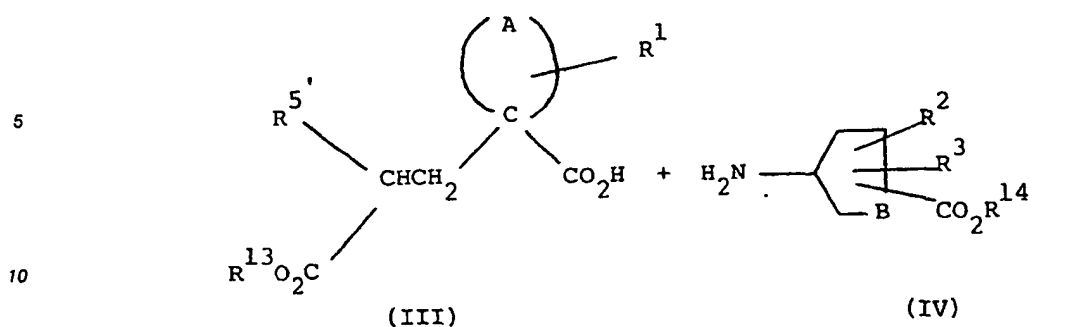
R<sup>11</sup> C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, Aryl oder Heterocyclyl ist;

R<sup>12</sup> H oder C<sub>1</sub>-C<sub>4</sub>-Alkyl bedeutet und

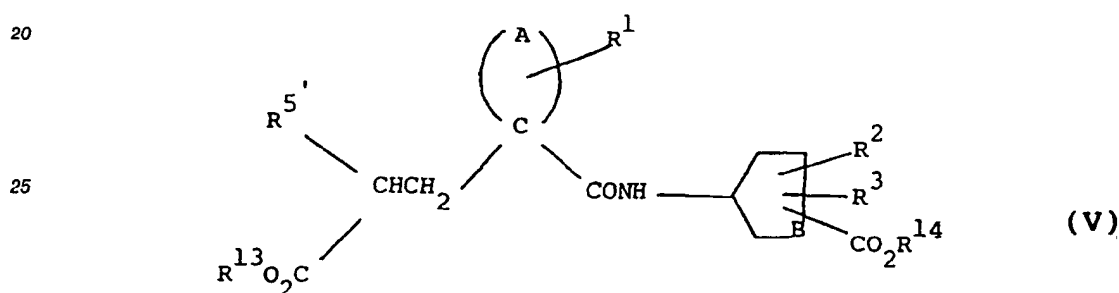
p Null, 1 oder 2 ist,

oder eines pharmazeutisch annehmbaren Salzes hiervon, das die folgenden Schritte umfaßt:

- a) Umsetzen von Verbindungen der Formeln



15 worin A, B, R<sup>1</sup>, R<sup>2</sup> und R<sup>3</sup> wie oben definiert sind, R<sup>5'</sup> wie für R<sup>5</sup> definiert ist, wobei jede reaktive Gruppe darin gegebenenfalls geschützt ist, und R<sup>13</sup> und R<sup>14</sup> wie für R und R<sup>4</sup> definiert sind, ausgenommen H, oder herkömmliche Carbonsäureschutzgruppen darstellen, wobei eine Verbindung der Formel



erhalten wird,

b) gegebenenfalls Unterwerfen des Produktes einer herkömmlichen chemischen Überführungsreaktion;

c) im Fall, daß eines oder beide von R<sup>13</sup> und R<sup>14</sup> unabhängig C<sub>1</sub>-C<sub>6</sub>-Alkyl oder Benzyl sind, Entfernen einer oder beider dieser Gruppen; oder im Fall, daß eine oder beide von R<sup>13</sup> und R<sup>14</sup> herkömmliche Carbonsäureschutzgruppen sind, Entfernen der Carbonsäureschutzgruppen; und im Fall, daß R<sup>5'</sup> eine Schutzgruppe enthält, Entfernen der Schutzgruppe, wobei die Verbindung der Formel (I) erhalten wird, worin R und R<sup>4</sup> beide H sind oder worin eines von R und R<sup>4</sup> H ist und das andere C<sub>1</sub>-C<sub>6</sub>-Alkyl, Benzyl oder eine alternative biolabile esterbildende Gruppe darstellt, und

d) gegebenenfalls Verestern des Produktes, worin eines von R<sup>13</sup> und R<sup>14</sup> C<sub>1</sub>-C<sub>6</sub>-Alkyl, Benzyl oder eine herkömmliche Carbonsäureschutzgruppe bedeutet und das andere H ist, mit einer biolabilen esterbildenden Gruppe, gefolgt von der Entfernung der C<sub>1</sub>-C<sub>6</sub>-Alkyl-, Benzyl- oder Carbonsäureschutzgruppe, wobei die Verbindung der Formel (I) erhalten wird, worin eines von R und R<sup>4</sup> eine biolabile esterbildende Gruppe bedeutet und das andere H ist; oder Verestern des Produktes der Formel (I), worin sowohl R als auch R<sup>4</sup> H bedeuten, mit einer biolabilen esterbildenden Gruppe, wobei das Produkt der Formel (I) erhalten wird, worin sowohl R als auch R<sup>4</sup> biolabile esterbildende Gruppen sind, und

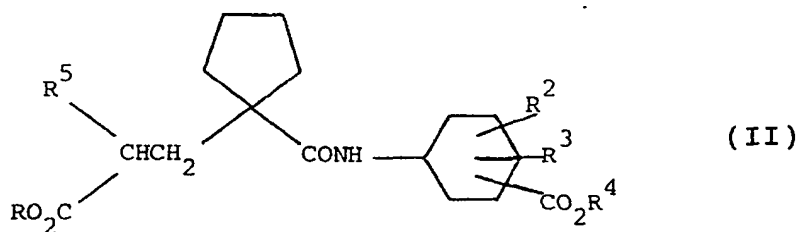
e) gegebenenfalls Bilden eines pharmazeutisch annehmbaren Salzes des Produktes.

50 2. Verfahren nach Anspruch 1, worin die Verbindungen der Formeln (III) und (IV) in einem organischen Lösungsmittel in Anwesenheit eines Diimidkondensationsmittels umgesetzt werden und das Mittel 1-Äthyl-3-(dimethylaminopropyl)-carbodiimid oder N,N'-Dicyclohexylcarbodiimid ist.

35 3. Verfahren nach Anspruch 1, worin sowohl R<sup>13</sup> als auch R<sup>14</sup> Benzyl sind oder worin eines Benzyl ist und das andere C<sub>1</sub>-C<sub>6</sub>-Alkyl oder eine alternative biolabile esterbildende Gruppe darstellt, und worin das Produkt der Formel (V) katalytischer Hydrierung unterworfen wird, wobei die Verbindung der Formel (I) erhalten wird, worin R und R<sup>4</sup> beide H sind oder worin eines H ist und das andere C<sub>1</sub>-C<sub>6</sub>-Alkyl bzw. eine alternative biolabile esterbildende Gruppe bedeutet, und worin das Produkt, wenn eines

von R und R<sup>4</sup> C<sub>1</sub>-C<sub>8</sub>-Alkyl ist, gegebenenfalls zur Verbindung der Formel (I), worin R und R<sup>4</sup> beide H sind, hydrolysiert wird.

4. Verfahren nach Anspruch 1, worin eines von R<sup>13</sup> und R<sup>14</sup> tert. Butyl ist und das andere Methyl, Äthyl oder Benzyl darstellt, und worin das Produkt der Formel (V) mit Trifluoressigsäure behandelt wird, wobei die Verbindung der Formel (I) erhalten wird, worin eines von R und R<sup>4</sup> H ist und das andere Methyl, Äthyl oder Benzyl darstellt, und worin das Produkt gegebenenfalls zur Verbindung der Formel (I), worin R und R<sup>4</sup> beide H sind, hydrolysiert oder hydriert wird.
5. Verfahren nach Anspruch 1, worin A die Bedeutung (CH<sub>2</sub>)<sub>n</sub> hat und n eine ganze Zahl von 3 bis 6 ist und worin jedes von R und R<sup>4</sup> unabhängig H, C<sub>1</sub>-C<sub>6</sub>-Alkyl oder Benzyl darstellt.
6. Verfahren nach Anspruch 1, worin A die Bedeutung (CH<sub>2</sub>)<sub>4</sub> hat, R<sup>1</sup> H darstellt und B (CH<sub>2</sub>)<sub>2</sub> ist, und die Verbindung der Formel (I) die Formel



aufweist, worin R, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> wie in Anspruch 1 definiert sind.

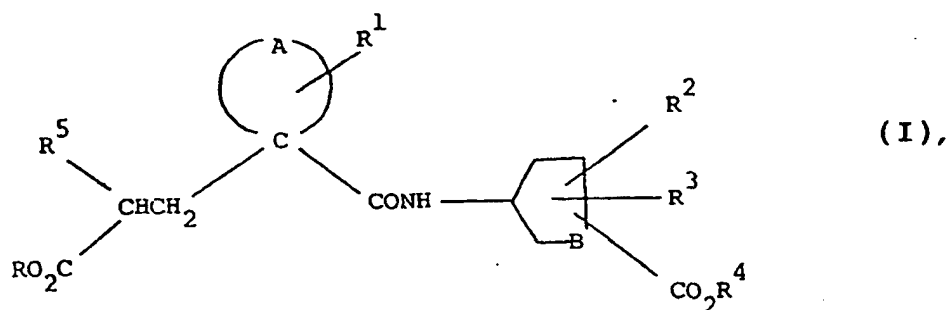
7. Verfahren nach Anspruch 1, worin die alternative biolabile esterbildende Gruppe 1-(2,2-Diäthylbutyryloxy)-äthyl, 2-Äthylpropionyloxymethyl, 1-(2-Äthylpropionyloxy)-äthyl, 1-(2,4-Dimethylbenzoyloxy)-äthyl, α-Benzoyloxybenzyl, 1-(Benzoyloxy)äthyl, 2-Methyl-1-propionyloxy-1-propyl, 2,4,6-Trimethylbenzoyloxymethyl, 1-(2,4,6-Trimethylbenzoyloxy)-äthyl, Pivaloyloxymethyl, Phenäthyl, Phenpropyl, 2,2,2-Trifluoräthyl, 1-oder 2-Naphthyl, 2,4-Dimethylphenyl, 4-tert. Butylphenyl oder 5-Indanyl ist.
8. Verfahren nach Anspruch 6, worin R, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> jeweils H sind und worin sich die Carboxygruppe CO<sub>2</sub>R<sup>4</sup> in Stellung 3 oder 4 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist.
9. Verfahren nach Anspruch 6, worin R, R<sup>2</sup> und R<sup>3</sup> jeweils H sind, R<sup>4</sup> die Bedeutung C<sub>2</sub>H<sub>5</sub> hat und worin sich die Äthoxycarbonylgruppe in Stellung 3 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist.
10. Verfahren nach einem vorhergehenden Anspruch, worin R<sup>5</sup> C<sub>2</sub>-C<sub>4</sub>-Alkyl, C<sub>2</sub>-C<sub>4</sub>-Alkenyl, C<sub>2</sub>-C<sub>5</sub>-Alkynyl, C<sub>5</sub>-C<sub>6</sub>-Cycloalkyl, C<sub>5</sub>-C<sub>6</sub>-Cycloalkenyl, C<sub>1</sub>-C<sub>4</sub>-Alkylsulfonamido oder Tetrahydrofuranyl bedeutet oder worin R<sup>5</sup> C<sub>1</sub>-C<sub>3</sub>-Alkyl substituiert durch C<sub>1</sub>-C<sub>3</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkoxy-(C<sub>2</sub>-C<sub>4</sub>-alkoxy), C<sub>3</sub>-C<sub>6</sub>-Cycloalkyl, 4-Pyridyl, 2-Imidazolyl, C<sub>2</sub>-C<sub>4</sub>-Alkanoyl, C<sub>2</sub>-C<sub>4</sub>-Alkoxycarbonylamino, C<sub>1</sub>-C<sub>4</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>4</sub>-Alkylsulfonamido, Arylsulfonamido, Heteroarylsulfonamido oder Benzoylamino darstellt.
11. Verfahren nach Anspruch 6, worin R und R<sup>4</sup> beide H bedeuten, R<sup>2</sup> und R<sup>3</sup> beide H darstellen, die Gruppe CO<sub>2</sub>R<sup>4</sup> sich in Stellung 4 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist und worin R<sup>5</sup> n-Propyl, Methoxyäthyl, 2-Methoxyäthoxymethyl, 2-Butinyl, 2-Cyclohexenyl, Tetrahydrofuranyl, 4-Pyridylmethyl, 2-Imidazolylmethyl, Acetonyl, Äthylsulfonylmethyl, Benzolsulfonamidomethyl, n-Propylsulfonamido oder 1-Methoxycarbonylaminoäthyl bedeutet.
12. Verfahren nach Anspruch 6, worin R und R<sup>4</sup> beide H bedeuten, R<sup>2</sup> und R<sup>3</sup> beide H darstellen, die Gruppe CO<sub>2</sub>R<sup>4</sup> sich in Stellung 3 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist und worin R<sup>5</sup> n-Propyl, 2-Methoxyäthoxymethyl, 2-Butinyl, 2-Propenyl, 2-Butenyl, Cyclopentyl, Cyclohexyl, 2-Cyclohexenyl, Cyclopropylmethyl, Tetrahydrofuranyl, 4-Pyridylmethyl, n-Propylsulfonamido, Benzolsulfonaminomethyl oder Benzoylaminomethyl ist.

13. Verfahren nach Anspruch 6, worin R<sup>1</sup> H bedeutet und R<sup>4</sup> Äthyl ist und worin R<sup>2</sup> und R<sup>3</sup> beide H darstellen, die Äthoxycarbonylgruppe sich in Stellung 3 des Cyclohexanringes befindet und cis-Stereochemie aufweist und worin R<sup>5</sup> 2-Methoxyäthoxymethyl, n-Propyl, 2-Butinyl, 2-Propenyl, Cyclohexenyl, Cyclohexyl, Cyclopentyl, Cyclopropylmethyl, Tetrahydrofuranyl, 4-Pyridylmethyl, Benzolsulfonamidomethyl, Benzoylaminomethyl oder n-Propylsulfonamido ist.

14. Verfahren nach Anspruch 6, worin R<sup>2</sup> und R<sup>3</sup> beide H sind, die Gruppe -CO<sub>2</sub>R<sup>4</sup> sich in Stellung 4 des Cyclohexanringes befindet und cis-Stereochemie aufweist, R<sup>5</sup> 2-Methoxyäthoxymethyl ist und entweder R<sup>1</sup> 5-Indanyl und R<sup>4</sup> H bedeuten oder R<sup>4</sup> 5-Indanyl und R<sup>1</sup> H sind.

#### Patentansprüche für folgenden Vertragsstaat : GR

##### 1. Verfahren zum Herstellen einer Verbindung der Formel



worin A einen 4- bis 7-gliedrigen carbocyclischen Ring vervollständigt, der gesättigt oder monounsättigt sein kann und der gegebenenfalls an einen weiteren gesättigten oder ungesättigten 5- oder 6-gliedrigen carbocyclischen Ring kondensiert sein kann;

B (CH<sub>2</sub>)<sub>m</sub> darstellt, wobei m eine ganze Zahl von 1 bis 3 ist;

jedes von R und R<sup>4</sup> unabhängig H, C<sub>1</sub>-C<sub>6</sub>-Alkyl, Benzyl oder eine alternative biolabile esterbildende Gruppe bedeutet;

R<sup>1</sup> H oder C<sub>1</sub>-C<sub>4</sub>-Alkyl ist;

R<sup>2</sup> und R<sup>3</sup> unabhängig jeweils H, OH, C<sub>1</sub>-C<sub>4</sub>-Alkyl oder C<sub>1</sub>-C<sub>4</sub>-Alkoxy bedeuten; und

R<sup>5</sup> C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>2</sub>-C<sub>6</sub>-Alkenyl, C<sub>2</sub>-C<sub>6</sub>-Alkynyl, Aryl-(C<sub>2</sub>-C<sub>6</sub>-alkynyl), C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkenyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup> oder eine gesättigte heterocyclische Gruppe darstellt oder C<sub>1</sub>-C<sub>8</sub>-Alkyl substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, Hydroxy, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>2</sub>-C<sub>8</sub>-Hydroxyalkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkoxy-(C<sub>1</sub>-C<sub>6</sub>-alkoxy), C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkenyl, Aryl, Aryloxy, Aryloxy-(C<sub>1</sub>-C<sub>4</sub>-alkoxy), Heterocyclyl, Heterocycloxy, -NR<sup>6</sup>R<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>, -CONR<sup>6</sup>R<sup>7</sup>, -SH, S(O)<sub>p</sub>R<sup>10</sup>, -COR<sup>11</sup> oder -CO<sub>2</sub>R<sup>12</sup> ist,

wobei R<sup>6</sup> und R<sup>7</sup> unabhängig jeweils H, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl (gegebenenfalls substituiert durch Hydroxy oder C<sub>1</sub>-C<sub>4</sub>-Alkoxy), Aryl, Aryl-(C<sub>1</sub>-C<sub>4</sub>-alkyl), C<sub>2</sub>-C<sub>6</sub>-Alkoxyalkyl oder Heterocyclyl sind oder die beiden Gruppen R<sup>6</sup> und R<sup>7</sup> zusammen mit dem Stickstoff, an den sie gebunden sind, eine Pyrrolidiny-, Piperidino-, Morpholino-, Piperaziny- oder N-(C<sub>1</sub>-C<sub>4</sub>-Alkyl)-piperazinygruppe bilden;

R<sup>8</sup> H oder C<sub>1</sub>-C<sub>4</sub>-Alkyl ist;

R<sup>9</sup> C<sub>1</sub>-C<sub>4</sub>-Alkyl, CF<sub>3</sub>, Aryl, Aryl-(C<sub>1</sub>-C<sub>4</sub>-alkyl), Aryl-(C<sub>1</sub>-C<sub>4</sub>-alkoxy), Heterocyclyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy oder NR<sup>6</sup>R<sup>7</sup> darstellt, wobei R<sup>6</sup> und R<sup>7</sup> wie oben definiert sind;

R<sup>10</sup> C<sub>1</sub>-C<sub>4</sub>-Alkyl, Aryl, Heterocyclyl oder NR<sup>6</sup>R<sup>7</sup> bedeutet, wobei R<sup>6</sup> und R<sup>7</sup> wie oben definiert sind;

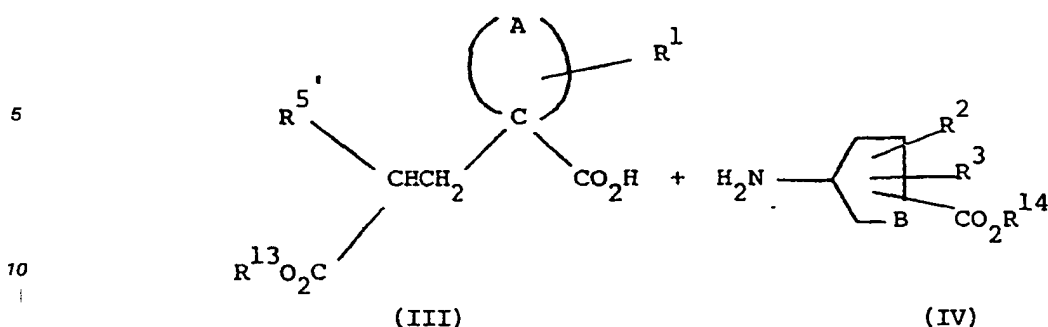
R<sup>11</sup> C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, Aryl oder Heterocyclyl ist;

R<sup>12</sup> H oder C<sub>1</sub>-C<sub>4</sub>-Alkyl bedeutet und

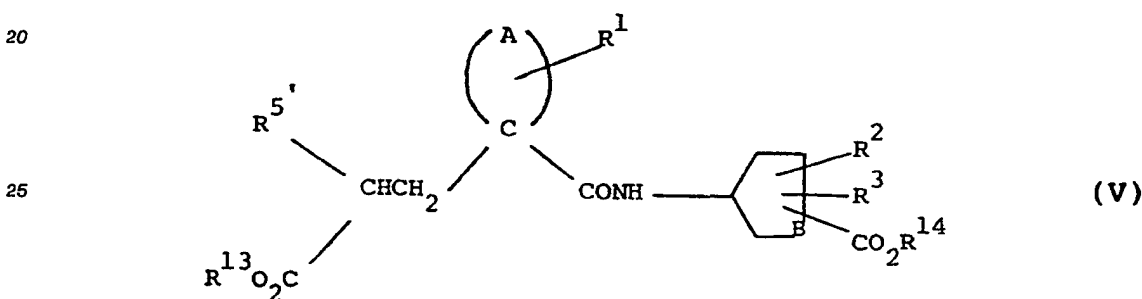
p Null, 1 oder 2 ist,

oder eines pharmazeutisch annehmbaren Salzes hiervon, das die folgenden Schritte umfaßt:

a) Umsetzen von Verbindungen der Formeln



15 worin A, B, R<sup>1</sup>, R<sup>2</sup> und R<sup>3</sup> wie oben definiert sind, R<sup>5'</sup> wie für R<sup>5</sup> definiert ist, wobei jede reaktive Gruppe darin gegebenenfalls geschützt ist, und R<sup>13</sup> und R<sup>14</sup> wie für R und R<sup>4</sup> definiert sind, ausgenommen H, oder herkömmliche Carbonsäureschutzgruppen darstellen, wobei eine Verbindung der Formel



- 30 erhalten wird,
- b) gegebenenfalls Unterwerfen des Produktes einer herkömmlichen chemischen Überföhrungsreaktion;
- 35 c) im Fall, daß eines oder beide von R<sup>13</sup> und R<sup>14</sup> unabhängig C<sub>1</sub>-C<sub>6</sub>-Alkyl oder Benzyl sind, Entfernen einer oder beider dieser Gruppen; oder im Fall, daß eine oder beide von R<sup>13</sup> und R<sup>14</sup> herkömmliche Carbonsäureschutzgruppen sind, Entfernen der Carbonsäureschutzgruppen; und im Fall, daß R<sup>5'</sup> eine Schutzgruppe enthält, Entfernen der Schutzgruppe, wobei die Verbindung der Formel (I) erhalten wird, worin R und R<sup>4</sup> beide H sind oder worin eines von R und R<sup>4</sup> H ist und das andere C<sub>1</sub>-C<sub>6</sub>-Alkyl, Benzyl oder eine alternative biolabile esterbildende Gruppe darstellt, und
- 40 d) gegebenenfalls Verestern des Produktes, worin eines von R<sup>13</sup> und R<sup>14</sup> C<sub>1</sub>-C<sub>6</sub>-Alkyl, Benzyl oder eine herkömmliche Carbonsäureschutzgruppe bedeutet und das andere H ist, mit einer biolabilen esterbildenden Gruppe, gefolgt von der Entfernung der C<sub>1</sub>-C<sub>6</sub>-Alkyl-, Benzyl- oder Carbonsäureschutzgruppe, wobei die Verbindung der Formel (I) erhalten wird, worin eines von R und R<sup>4</sup> eine biolabile esterbildende Gruppe bedeutet und das andere H ist; oder Verestern des Produktes der
- 45 Formel (I), worin sowohl R als auch R<sup>4</sup> H bedeuten, mit einer biolabilen esterbildenden Gruppe, wobei das Produkt der Formel (I) erhalten wird, worin sowohl R als auch R<sup>4</sup> biolabile esterbildende Gruppen sind, und
- e) gegebenenfalls Bilden eines pharmazeutisch annehmbaren Salzes des Produktes.

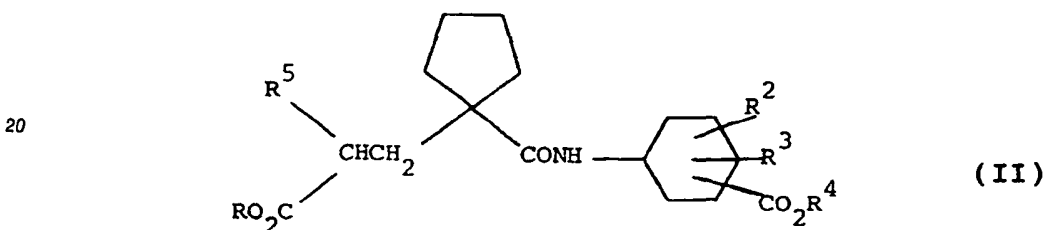
- 50 2. Verfahren nach Anspruch 1, worin die Verbindungen der Formeln (III) und (IV) in einem organischen Lösungsmittel in Anwesenheit eines Diimidkondensationsmittels umgesetzt werden und das Mittel 1-Äthyl-3-(dimethylaminopropyl)-carbodiimid oder N,N'-Dicyclohexylcarbodiimid ist.
3. Verfahren nach Anspruch 1, worin sowohl R<sup>13</sup> als auch R<sup>14</sup> Benzyl sind oder worin eines Benzyl ist und das andere C<sub>1</sub>-C<sub>6</sub>-Alkyl oder eine alternative biolabile esterbildende Gruppe darstellt, und worin das Produkt der Formel (V) katalytischer Hydrierung unterworfen wird, wobei die Verbindung der Formel (I) erhalten wird, worin R und R<sup>4</sup> beide H sind oder worin eines H ist und das andere C<sub>1</sub>-C<sub>6</sub>-Alkyl bzw. eine alternative biolabile esterbildende Gruppe bedeutet, und worin das Produkt, wenn eines



von R und R<sup>4</sup> C<sub>1</sub>-C<sub>6</sub>-Alkyl ist, gegebenenfalls zur Verbindung der Formel (I), worin R und R<sup>4</sup> beide H sind, hydrolysiert wird.

4. Verfahren nach Anspruch 1, worin eines von R<sup>13</sup> und R<sup>14</sup> tert. Butyl ist und das andere Methyl, Äthyl oder Benzyl darstellt, und worin das Produkt der Formel (V) mit Trifluoressigsäure behandelt wird, wobei die Verbindung der Formel (I) erhalten wird, worin eines von R und R<sup>4</sup> H ist und das andere Methyl, Äthyl oder Benzyl darstellt, und worin das Produkt gegebenenfalls zur Verbindung der Formel (I), worin R und R<sup>4</sup> beide H sind, hydrolysiert oder hydriert wird.
5. Verfahren nach Anspruch 1, worin A die Bedeutung (CH<sub>2</sub>)<sub>n</sub> hat und n eine ganze Zahl von 3 bis 6 ist und worin jedes von R und R<sup>4</sup> unabhängig H, C<sub>1</sub>-C<sub>6</sub>-Alkyl oder Benzyl darstellt.
6. Verfahren nach Anspruch 1, worin A die Bedeutung (CH<sub>2</sub>)<sub>4</sub> hat, R<sup>1</sup> H darstellt und B (CH<sub>2</sub>)<sub>2</sub> ist, und die Verbindung der Formel (I) die Formel

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aufweist, worin R, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> und R<sup>5</sup> wie in Anspruch 1 definiert sind.

7. Verfahren nach Anspruch 1, worin die alternative biolabile esterbildende Gruppe 1-(2,2-Diäthylbutyryloxy)-äthyl, 2-Äthylpropionyloxymethyl, 1-(2-Äthylpropionyloxy)-äthyl, 1-(2,4-Dimethylbenzoyloxy)-äthyl, α-Benzoyloxybenzyl, 1-(Benzoyloxy)-äthyl, 2-Methyl-1-propionyloxy-1-propyl, 2,4,6-Trimethylbenzoyloxymethyl, 1-(2,4,6-Trimethylbenzoyloxy)-äthyl, Pivaloyloxymethyl, Phenäthyl, Phenpropyl, 2,2,2-Trifluoräthyl, 1-oder 2-Naphthyl, 2,4-Dimethylphenyl, 4-tert. Butylphenyl oder 5-Indanyl ist.
8. Verfahren nach Anspruch 6, worin R, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> jeweils H sind und worin sich die Carboxygruppe CO<sub>2</sub>R<sup>4</sup> in Stellung 3 oder 4 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist.
9. Verfahren nach Anspruch 6, worin R, R<sup>2</sup> und R<sup>3</sup> jeweils H sind, R<sup>4</sup> die Bedeutung C<sub>2</sub>H<sub>5</sub> hat und worin sich die Äthoxycarbonylgruppe in Stellung 3 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist.
10. Verfahren nach einem vorhergehenden Anspruch, worin R<sup>5</sup> C<sub>2</sub>-C<sub>4</sub>-Alkyl, C<sub>2</sub>-C<sub>4</sub>-Alkenyl, C<sub>2</sub>-C<sub>5</sub>-Alkynyl, C<sub>5</sub>-C<sub>6</sub>-Cycloalkyl, C<sub>5</sub>-C<sub>6</sub>-Cycloalkenyl, C<sub>1</sub>-C<sub>4</sub>-Alkylsulfonamido oder Tetrahydrofuranyl bedeutet oder worin R<sup>5</sup> C<sub>1</sub>-C<sub>3</sub>-Alkyl substituiert durch C<sub>1</sub>-C<sub>3</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkoxy-(C<sub>2</sub>-C<sub>4</sub>-alkoxy), C<sub>3</sub>-C<sub>6</sub>-Cycloalkyl, 4-Pyridyl, 2-Imidazolyl, C<sub>2</sub>-C<sub>4</sub>-Alkanoyl, C<sub>2</sub>-C<sub>4</sub>-Alkoxycarbonylamino, C<sub>1</sub>-C<sub>4</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>4</sub>-Alkylsulfonamido, Arylsulfonamido, Heteroarylsulfonamido oder Benzoylamino darstellt.
11. Verfahren nach Anspruch 6, worin R und R<sup>4</sup> beide H bedeuten, R<sup>2</sup> und R<sup>3</sup> beide H darstellen, die Gruppe CO<sub>2</sub>R<sup>4</sup> sich in Stellung 4 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist und worin R<sup>5</sup> n-Propyl, Methoxyäthyl, 2-Methoxyäthoxymethyl, 2-Butinyl, 2-Cyclohexenyl, Tetrahydrofuranyl, 4-Pyridylmethyl, 2-Imidazolylmethyl, Acetonyl, Äthylsulfonylmethyl, Benzolsulfonamidomethyl, n-Propylsulfonamido oder 1-Methoxycarbonylaminoäthyl bedeutet.
12. Verfahren nach Anspruch 6, worin R und R<sup>4</sup> beide H bedeuten, R<sup>2</sup> und R<sup>3</sup> beide H darstellen, die Gruppe CO<sub>2</sub>R<sup>4</sup> sich in Stellung 3 des Cyclohexanringes befindet und in bezug auf die Amidgruppe cis-Stereochemie aufweist und worin R<sup>5</sup> n-Propyl, 2-Methoxyäthoxymethyl, 2-Butinyl, 2-Propenyl, 2-Butenyl, Cyclopentyl, Cyclohexyl, 2-Cyclohexenyl, Cyclopropylmethyl, Tetrahydrofuranyl, 4-Pyridylmethyl, n-Propylsulfonamino, Benzolsulfonylaminomethyl oder Benzoylaminomethyl ist.

13. Verfahren nach Anspruch 6, worin R H bedeutet und R<sup>4</sup> Äthyl ist und worin R<sup>2</sup> und R<sup>3</sup> beide H darstellen, die Äthoxycarbonylgruppe sich in Stellung 3 des Cyclohexanringes befindet und cis-Stereochemie aufweist und worin R<sup>5</sup> 2-Methoxyäthoxymethyl, n-Propyl, 2-Butinyl, 2-Propenyl, Cyclohexenyl, Cyclohexyl, Cyclopentyl, Cyclopropylmethyl, Tetrahydrofuranlyl, 4-Pyridylmethyl, Benzolsulfonamidomethyl, Benzoylaminomethyl oder n-Propylsulfonamido ist.
14. Verfahren nach Anspruch 6, worin R<sup>2</sup> und R<sup>3</sup> beide H sind, die Gruppe -CO<sub>2</sub>R<sup>4</sup> sich in Stellung 4 des Cyclohexanringes befindet und cis-Stereochemie aufweist, R<sup>5</sup> 2-Methoxyäthoxymethyl ist und entweder R 5-Indanyl und R<sup>4</sup> H bedeuten oder R<sup>4</sup> 5-Indanyl und R H sind.
15. Verbindung der Formel (V), wie in Anspruch 1 definiert.